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(54) Title: SUGAR ALCOHOL DERIVATIVES, A PROCESS FOR PREPARING 3-DEOXY-2-OCTULOSONIC ACID AND 3-DEOXY-2-HEPTULOSONIC ACID COMPOUNDS AND DERIVATIVES

(57) Abstract

The invention provides a novel class of versatile intermediates, i.e. 1,4 cyclic sulfates of sugar alcohols having protected hydroxy groups, such as 1,4 cyclic sulfates of D-mannitol having protected 2-, 3-, 5- and 6-hydroxy groups and D-arabinitol having protected 2-, 3- and 5-hydroxy groups. The invention also provides methods for preparing 3-deoxy-2-octulosonic acid and 3-deoxy-2-heptulosonic acid compounds and derivatives, in which these novel 1,4 cyclic sulfates are used as intermediates.

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Title: sugar alcohol derivatives, a process for preparing 3-deoxy-2-octulosonic acid and 3-deoxy-2-heptulosonic acid compounds and derivatives

This invention relates to novel derivatives of sugar alcohols, such as, in particular, D-mannitol and D-arabinitol, and to processes for preparing 3-deoxy-2-octulosonic acid and 3-deoxy-2-heptulosonic acid compounds and derivatives, such as, in particular, 3-deoxy-D-manno-2-octulosonic acid and 3-deoxy-D-arabino-2-heptulosonic acid compounds and derivatives.

In one particular aspect, this invention relates to a process for preparing 3-deoxy-D-manno-2-octulosonic acid of formula 1, or an salt or ester thereof, which comprises reacting a D-mannitol derivative with the anion of a dithioacetal compound of a glyoxylic acid ester, then removing the dithioacetal group and hydroxy-protecting groups and, if desired, converting the resulting ester into the free acid, a salt or another ester of 3-deoxy-D-manno-2-octulosonic acid.

Such a process is known from an article by Imoto et al. in Tetrahedron Letters, 28, 6235 (1987). The crucial step of the process described therein for preparing 3-deoxy-D-manno-2-octulosonic acid of formula 1, which compound is known as KDO, is shown in the right-hand part of reaction scheme A of the sheet of formulae and consists in a nucleophilic displacement of a triflate group (i.e., a trifluoromethanesulfonyloxy group) at C-1 of the D-mannitol derivative 1-O-trifluoromethylsulfonyl-4-O-acetyl-2,3:5,6-di-O-isopropylidene-D-mannitol (formula 4) by the anion of the methylglyoxylate

dithioacetal compound of formula 5. After removal of the hydroxy-protecting acetyl group and of the used dithioacetal group the methyl ester of 4,5:7,8-di-O-isopropylidene-3-deoxy-D-manno-2-octulosonic acid is obtained by this known process in a yield of 42%, calculated on the methylglyoxylate dithioacetal compound of formula 5.

As compared with many of the earlier proposed processes for preparing KDO via an aldol- or Wittig-type reaction, this known preparation method on the basis of a nucleophilic substitution reaction has the significant advantage that only the required D-*manno* configuration is formed and not also the undesirable D-*gluco* configuration. The process, however, also has significant drawbacks, including, more in particular, the fact that the starting compounds are rather difficult to obtain. The D-mannitol derivative of formula 4 must be prepared from 2,3:5,6-di-O-isopropylidene-D-mannitol by first temporarily protecting the primary hydroxy group at C-1 with a 2,2,2-trichloroethoxycarbonyl group (Troc), then acetylating the hydroxy group at C-4, subsequently removing again the temporary hydroxy-protecting Troc group at C-1 and finally fluoromethanesulfonylating the released hydroxy group. For production on a larger scale such a laborious synthesis means a serious drawback. The methylglyoxylate dithioacetal compound of formula 5 to be converted with the thus prepared D-mannitol derivative must be prepared from glyoxylic acid and the rather eccentric compound 1,2-dimethyl-4,5-bis (mercaptomethyl) benzene.

The present invention provides a process with which the above drawbacks can be removed without having to accept again the simultaneous formation of the D-*gluco* configuration. In addition, the present invention provides a new and versatile intermediate compound.

The process according to the invention is characterized by using as the D-mannitol derivative 1,4 cyclic sulfate of D-mannitol with protected 2-, 3-, 5- and 6-hydroxy groups. According to the invention it is specifically preferred that the D-mannitol derivative used is the 1,4 cyclic sulfate of 2,3:5,6-di-O-isopropylidene-D-mannitol of formula 2. The new and versatile intermediate of the invention is a 1,4 cyclic sulfate of D-mannitol with protected 2-, 3-, 5- and 6-hydroxy groups.

The invention is also applicable to other sugar alcohols, however, and comprises more broadly a 1,4 cyclic sulfate of a sugar alcohol having protected hydroxy groups. Examples of such other sugar alcohols are the pentitols arabinitol, xylitol, lyxitol and ribitol, and the hexitols gulitol, glucitol, iditol, galactitol, talitol, altritol and allitol. In addition to 1,4 cyclic sulfate of mannitol having protected 2-, 3-, 5- and 6-hydroxy groups, the 1,4 cyclic sulfate of arabinitol having protected 2-, 3- and 5-hydroxy groups is also a preferred compound according to the invention. It is specifically preferred that the D-arabinitol derivative is the 1,4 cyclic sulfate of 2,3,5-tri-O-benzyl-D-arabinitol of formula 27.

As regards the other reactant, it is preferred according to the invention that the sugar alcohol derivative is reacted with the anion of a dithioacetal compound of a (C_1-C_4) alkyl or benzyl ester of glyoxylic acid. Very suitable esters are, e.g., the methyl, ethyl and benzyl ester.

A special preferred embodiment of the process according to the invention is characterized in that the sugar alcohol derivative is reacted with the anion of a 1,3-dithiane-2-carboxylic acid ester, preferably with the anion of ethyl 1,3-dithiane-2-carboxylate of formula 3.

The invention, a concrete preferred embodiment of which is shown in the left-hand part of reaction scheme A, is based to a very substantial degree on the realisation of a new type of compound, which compound due to its special properties is eminently suited for use as an intermediate in a large-scale process for preparing compounds like the important KDO and, as will be explained hereinafter in more detail, for preparing several interesting KDO derivatives. This new type of compound is a 1,4 cyclic sulfate of a sugar alcohol like D-mannitol with protected hydroxy groups, such as protected 2-, 3-, 5- and 6-hydroxy groups in the case of a hexitol and protected 2-, 3- and 5-hydroxy groups in the case of a pentitol, the 1,4 cyclic sulfate of 2,3:5,6-di-O-isopropylidene-D-mannitol of formula 2 and the 1,4 cyclic sulfate of 2,3,5-tri-O-benzyl-D-arabinitol representing preferred embodiments.

It is true that cyclic sulfate derivatives of carbohydrates have been described before, including their utility

as reactants in a nucleophilic displacement reaction, but these were only vicinal cyclic sulfates. In this connection reference may be made to articles by Tewson, J.Org. Chem. 48, 3507 (1983); Tewson and Soderlind, Carbohydr. Chem. 4, 529 (1985); Gao and Sharpless, J. Am. Chem. Soc. 110, 7538 (1988); Kim and Sharpless, Tetrahedron Lett. 30, 655 (1989); and Gao and Sharpless, Tetrahedron Lett. 30, 2623 (1989). The possibility of preparing non-vicinal cyclic sulfates of carbohydrates, such as a 1,4 cyclic sulfate of D-mannitol or of a D-mannitol derivative, or a 1,4 cyclic sulfate of D-arabinitol or of a D-arabinitol derivative, could not be derived from the literature.

Besides, the present invention is based not only on the surprising discovery that such 1,4 cyclic sulfates can be made, but also on the surprising established fact that they allow a very selective displacement reaction by means of a nucleophilic agent at C-1. In the reaction with a nucleophilic agent the sulfate ring is opened, with the sulfate group selectively remaining at C-4 and the nucleophilic agent being bound to C-1. Such a high reaction selectivity of 1,4 cyclic sulfates of carbohydrates could of course not be taken from the literature either.

An important advantage of 1,4 cyclic sulfates of sugar alcohols with protected hydroxy groups, such as 1,4 cyclic sulfate of 2,3:5,6-di-O-isopropylidene-D-mannitol of formula 2, is that they can be very easily prepared in high yield. Although other preparation methods are also eligible, it is

preferred according to the invention that 1,4 cyclic sulfate of D-mannitol with protected 2-, 3-, 5- and 6-hydroxy groups is prepared by reacting D-mannitol, the 2-, 3-, 5- and 6-hydroxy groups of which are protected, with thionyl chloride in the presence of an acid-binding agent and oxidizing the resulting 1,4 cyclic sulfite to the corresponding 1,4 cyclic sulfate. Thus the invention more in particularly also provides a process for preparing a 2,3:5,6-di-O-isopropylidene-D-mannitol derivative, which process is characterized in that 1,4 cyclic sulfate of 2,3:5,6-di-O-isopropylidene-D-mannitol of formula 2 is prepared by reacting 2,3:5,6-di-O-isopropylidene-D-mannitol with thionyl chloride in the presence of an acid-binding agent and oxidizing the resulting 1,4 cyclic sulfite to the corresponding 1,4 cyclic sulfate. This process is schematically shown in reaction scheme B on the sheet of formulae. The same process may be used for the preparation of the 1,4 cyclic sulfate of other sugar alcohols having protected hydroxy groups, such as the 1,4 cyclic sulfate of D-arabinitol having protected 2-, 3- and 5-hydroxy groups. Therefore, in a broad sense, the invention provides a process for preparing a 1,4 cyclic sulfate of a sugar alcohol having protected hydroxy groups, in which a sugar alcohol having free 1- and 4-hydroxy groups, its remaining hydroxy groups being protected, is reacted with thionyl chloride in the presence of an acid binding agent and the resulting 1,4 cyclic sulfite is oxidized to the corresponding 1,4 cyclic sulfate.

This process admits that the first reactant required for the nucleophilic displacement reaction is immediately prepared in two steps from an easily accessible sugar alcohol having its hydroxy groups protected except at carbon atoms 1 and 4, such as D-mannitol with protected 2-, 3-, 5- and 6-hydroxy groups and D-arabinitol with protected 2-, 3- and 5-hydroxy groups, without a necessity of time-consuming and yield-reducing reactions for protecting the hydroxy group at C-4 and (temporarily) the hydroxy group at C-1. Such an easily accessible D-mannitol with protected 2-, 3-, 5- and 6-hydroxy groups is, e.g., 2,3:5,6-di-O-isopropylidene-D-mannitol, which can be obtained in high yield by reduction of 2,3:5,6-di-O-isopropylidene-D-mannose with $NaBH_4$ (Austin et al., J. Chem. Soc. 2128 (1964). Another example of an easily accessible sugar alcohol having protected hydroxy groups at the correct places is 2,3,5-tri-O-benzyl-D-arabinitol of formula 25, which compound can be made from D-arabinose by transforming same under Fischer conditions to methyl α(β)-D-arabinofuranoside, benzylating this compound to obtain the compound of formula 24 as a mixture of anomers, followed by acetolysis and finally reduction with sodium borohydride. This procedure and the next steps to be carried out to obtain the 1,4 cyclic sulfate are depicted schematically in reaction scheme J.

In a first step of the above-described process for preparing a 1,4 cyclic sulfate of, e.g., 2,3:5,6-di-O-isopropylidene-D-mannitol a 1,4 cyclic sulfite is formed by reacting the 2,3:5,6-di-O-isopropylidene-D-mannitol with

thionyl chloride in the present of an acid-binding agent. To this end, the thionyl chloride is preferably added dropwise to a cooled (preferably below 0°C, such as -15°C) solution (e.g., in a solvent, such as methylene dichloride) containing a suitable acid-binding agent (e.g., triethylamine). A direct conversion of 2,3:5,6-di-O-isopropylidene-D-mannitol into the 1,4 cyclic sulfate by treatment with sulfuryl chloride fails owing to a tetrahydrofuran derivative being formed.

In a second step the 1,4 cyclic sulfite obtained in the first step is oxidized to the corresponding 1,4 cyclic sulfate, preferably after work-up and purification. For this purpose the catalytic RuO_4 system described by Gao and Sharpless in J. Am. Chem. Soc. 110, 7538 (1988) can be used (i.e. treatment with $NaIO_4$ and $RuCl_3$, e.g., in a mixture of methylene dichloride, acetonitrile and water).

The second reactant of the process according to the invention for preparing a 3-deoxy-2-octulosonic acid compound or a 3-deoxy-2-heptulosonic acid compound, such as 3-deoxy-D-manno-2-octulosonic acid (formula 1), consists of the anion of a dithioacetal compound of a glyoxylic acid ester. For this purpose, e.g., the anion of the methyl glyoxylate dithioacetal compound of formula 5 as used by Imoto et al. can be selected [the anion is formed in situ by treatment with butyl lithium in the presence of hexamethylphosphortriamide (HMPA)], but according to a preferred embodiment of the invention the anion of a 1,3-dithiane-2-carboxylic acid ester is used, e.g., methyl, ethyl or benzyl 1,3-dithiane-2-carboxylate. This type

of dithioacetal compound of glyoxylic acid esters can be easily prepared by conversion of diethoxyacetic acid ester with propane-1,3-dithiol (Eliel and Hartmann, J. Org. Chem. 37, 505 (1972)). This conversion is schematically shown in reaction scheme C on the sheet of formulae.

As appears from reaction scheme D, an intermediate product (formula 11) carrying a sulfate group to be removed is obtained in the conversion of the anion of a 1,3-dithiane-2-carboxylic acid ester (formula 8) with the 1,4 cyclic sulfate of 2,3:5,6-di-O-isopropylidene-D-mannitol of formula 2. After hydrolysis of the sulfate group (by adding a sulphuric acid solution, as described by Kim and Sharpless, Tetrahedron Letters 30, 655 (1989)) the resulting intermediate product of formula 12 can be liberated (preferably after work-up and purification) from the dithioacetal group by treatment with N-bromosuccinimide (NBS), e.g., in a mixture of acetone and water, whereby the KDO derivative of formula 13 is obtained. Removal of the two hydroxy-protecting isopropylidene groups can be realized by acidolysis with a mixture of acetic acid and water.

The resulting ester can be converted to the free acid by known per se methods (by basic hydrolysis),to salts thereof (especially alkali metal and ammonium salts) or to another ester (as far as the desired ester group is not already present in the starting material of formula 8).

From the thus obtained KDO there can be prepared interesting derivatives of KDO, such as the α-ketopyranosyl

fluoride (see Imoto et al., Tetrahedron Lett. 28, 6277, 1987), 1987) and the KDO glycal of formula 17, in which R and R^1–R^4 represent hydrogen atoms (see Norbeck et al., J. Org. Chem. 52, 2174, 1987). Furthermore the 2-thio-α-glycoside of formula 16 interesting as glycosyl donor, in which R and R^1–R^4 represent hydrogen atoms, could be prepared from the KDO by using the two-step procedure as described by Marra and Sinay, Carbohydr. Res. 195, 303, 1990, for the synthesis of a 2-thioglycoside of N-acetylneuraminic ester.

The present invention, however, surprisingly gives the possibility of directly preparing several of these interesting KDO derivatives, i.e. without first having to synthesize the KDO itself.

Thus the invention also comprises a process for preparing a 3-deoxy-D-manno-2-octulosonic acid derivative of formula 23, or an acid or ester thereof, in which R is a hydrogen atom, an ester group or a kation, R^1–R^4 independently of each other stand for hydrogen atoms or hydroxy-protecting groups, and R^6 is an alkyl group having 1-6 carbon atoms, a phenyl group or a benzyl group, which process is characterized in that a 1,4 cyclic sulfate of D-mannitol with protected 2-, 3-, 5- and 6-hydroxy groups is reacted with the anion of a glyoxylic acid ester dithioacetal compound of formula 21, in which R is an ester group and R^6 an alkyl group having 1-6 carbon atoms, a phenyl group or a benzyl group, to form a compound of formula 22, in which R and R^6 have the above meanings and R^1–R^4 are hydroxy protecting groups, which compound of formula 22 is

cyclized using iodonium ions to form a compound of formula 23, optionally removing the hydroxy protecting groups or replacing them by other hydroxy protecting groups and optionally converting the resulting ester into the free acid, a salt or another ester.

A preferred embodiment of this process is characterized in that the 1,4 cyclic sulfate of 2,3:5,6-di-O-isopropylidene-D-mannitol of formula 2 is reacted with a glyoxylic acid ester dithioacetal compound of formula 14, in which R is an ester group, to form a compound of formula 15 which is cyclized by means of N-iodosuccinimide to form a compound of formula 16, in which R^1+R^2 and R^3+R^4 are hydroxy-protecting isopropylidene groups and R is an ester group, and optionally removing the hydroxy-protecting groups or replacing them by other hydroxy-protecting groups and optionally converting the resulting ester into the free acid, a salt or another ester. This preferred embodiment of the invention is shown in reaction schemes E and F.

Furthermore, the invention also comprises a process for preparing a 2,6-anhydro-2,3-dideoxy-D-manno-2-octenoic acid compound of formula 17, or a salt or ester thereof, in which R is a hydrogen atom, an ester group or a cation and R^1-R^4 independently of each other stand for hydrogen atoms or hydroxy-protecting groups, which process is characterized according to the invention in that a 1,4 cyclic sulfate of D-mannitol with protected 2-, 3-, 5- and 6-hydroxy groups is reacted with the anion of a glyoxylic acid ester dithioacetal

compound of formula 21 in which R is an ester group and R^6 an alkyl group having 1-6 carbon atoms, a phenyl group or a benzyl group, to form a compound of formula 22, in which R and R^6 have the above meanings and R^1-R^4 are hydroxy-protecting groups, cyclizing this compound of formula 22 using iodonium ions to form a compound of formula 17, optionally removing the hydroxy-protecting groups or replacing them by other hydroxy-protecting groups and optionally converting the resulting ester into the free acid, a salt or another ester.

A preferred embodiment of this process is characterized in that the 1,4 cyclic sulfate of 2,3:5,6-di-O-isopropylidene-D-mannitol of formula 2 is reacted with a glyoxylic acid ester dithioacetal compound of formula 14, in which R is an ester group, to form a compound of formula 15 which is cyclized by means of iodonium sym-dicollidine perchlorate to a compound of formula 17, in which R^1+R^2 and R^3+R^4 are hydroxy-protecting isopropylidene groups and R is an ester group, optionally removing the hydroxy-protecting groups or replacing them by other hydroxy-protecting groups and optionally converting the resulting ester into the free acid, a salt or another ester. This preferred process is shown in reaction schemes E and G.

In a broader sense, however, the invention provides a process for preparing a 3-deoxy-2-octulosonic acid compound or a 3-deoxy-2-heptulosonic acid compound having protected or unprotected hydroxy groups, or a salt or ester thereof, which comprises reacting either a 1,4 cyclic sulfate of a hexitol having protected 2-, 3-, 5- and 6-hydroxy groups or a 1,4

cyclic sulfate of a pentitol having protected 2-, 3- and 5-hydroxy groups, with the anion of a dithioacetal compound of a glyoxylic acid ester, hydrolysing the sulfate group, removing the dithioacetal group, optionally removing the hydroxy protecting groups and optionally converting the resulting ester into the free acid, a salt or another ester of the 3-deoxy-2-octulosonic acid or 3-deoxy-2-heptulosonic acid compound.

A further example of such a process is constituted by a process for preparing a 3-deoxy-D-arabino-2-heptulosonic acid compound of formula 39 having protected or unprotected hydroxy groups, or a salt or ester thereof, which comprises reacting a 1,4 cyclic sulfate of a D-arabinitol having protected 2-, 3- and 5-hydroxy groups with the anion of a dithioacetal compound of a glyoxylic acid ester, hydrolysing the sulfate group, removing the dithioacetal group, optionally removing the hydroxy protecting groups and optionally converting the resulting ester into the free acid, a salt or another ester of the 3-deoxy-D-arabino-2-heptulosonic acid compound. It is preferred that 1,4 cyclic sulfate of 2,3,5-tri-O-benzyl-D-arabinitol of formula 27 is used as the 1,4 cyclic sulfate of a D-arabinitol having protected 2-, 3- and 5-hydroxy groups. This reaction is depicted schematically in reaction scheme K.

In a broad sense, the invention also provides a process for preparing a 3-deoxy-2-thio-2-octulosonic acid derivative or a 3-deoxy-2-thio-2-heptulosonic acid derivative, or a salt or ester thereof, in which derivative the hydroxy group

attached to the carbon atom at position 2 is replaced by a thio group $-SR^6$, wherein R^6 is an alkyl group having 1-6 carbon atoms, a phenyl group or a benzyl group, in which process either a 1,4 cyclic sulfate of a D-hexitol having protected 2-, 3-, 5- and 6-hydroxy groups or a 1,4 cyclic sulfate of a D-pentitol having protected 2-, 3- and 5-hydroxy groups, is reacted with the anion of a glyoxylic acid ester dithioacetal compound of formula 21, in which R is an ester group and R^6 an alkyl group having 1-6 carbon atoms, a phenyl group or a benzyl group, to form, after hydrolysis of the sulfate group, either a 3-deoxy-octulonate dithioacetal compound having protected 4-,5-,7- and 8-hydroxy groups, or a 3-deoxy-heptulonate dithioacetal compound having protected 4-, 5- and 7-hydroxy groups, which compound is cyclized using iodonium ions to form a 3-deoxy-2-thio-2-octulosonic acid ester having protected hydroxy groups or a 3-deoxy-2-thio-2-heptulosonic acid ester having protected hydroxy groups, optionally removing the hydroxy protecting groups or replacing them by other hydroxy protecting groups and optionally converting the resulting ester into the free acid, a salt or another ester.

A further process comprised by this invention is in more general terms a process for preparing a 2,6-anhydro-2,3-dideoxy-2-octenoate compound or a 2,6-anhydro-2,3-dideoxy-2-heptenoate compound, or a salt or ester thereof, in which process either a 1,4 cyclic sulfate of a D-hexitol having protected 2-, 3-, 5- and 6-hydroxy groups or a 1,4 cyclic sulfate of a D-pentitol having protected 2-, 3- and 5-hydroxy

groups, is reacted with the anion of a glyoxylic acid ester dithioacetal compound of formula 21, in which R is an ester group and R^6 is an alkyl group having 1-6 carbon atoms, a phenyl group or a benzyl group, to form, after hydrolysis of the sulfate group, either a 3-deoxy-octulonate dithioacetal compound having protected 4-,5-,7- and 8-hydroxy groups, or a 3-deoxy-heptulonate dithioacetal compound having protected 4-, 5- and 7-hydroxy groups, which compound is cyclized using iodonium ions to form a 2,6-anhydro-2,3-dideoxy-2-octenoate ester having protected hydroxy groups or a 2,6-anhydro-2,3-dideoxy-2-heptenoate ester having protected hydroxy groups, optionally removing the hydroxy protecting groups or replacing them by other hydroxy protecting groups and optionally converting the resulting ester into the free acid, a salt or another ester.

In general terms, the invention also provides a process for preparing a 2-deoxy-heptopyranose compound or a 2-deoxy-hexopyranose compound, which process comprises reacting either a 1,4 cyclic sulfate of a D-hexitol having protected 2-, 3-, 5- and 6-hydroxy groups or a 1,4 cyclic sulfate of a D-pentitol having protected 2-, 3- and 5-hydroxy groups, with the anion of a bis (hydrocarbylthio) methane compound, in which the hydrocarbyl group is an alkyl group having 1-6 carbon atoms, a phenyl group or a benzyl group, to form, after hydrolysis of the sulfate group, either a 2-deoxy-heptose bis (hydrocarbylthio) acetal compound having protected 3-,4-,6- and 7-hydroxy groups, or a 2-deoxy-hexose bis (hydrocarbyl-

thio) acetal compound having protected 3-, 4- and 6-hydroxy groups, followed by removal of the dithioacetal group to form a 2-deoxy-heptopyranose compound having protected 3-,4-,6- and 7-hydroxy groups or a 2-deoxy-hexopyranose compound having protected 3-, 4- and 6-hydroxy groups, and optionally removing the hydroxy protecting groups or replacing them by other hydroxy protecting groups.

As a more specific example of such a process the invention provides a process for preparing a 2-deoxy-α/β-D-arabino-hexopyranose compound, which process comprises reacting a 1,4 cyclic sulfate of a D-arabinitol having protected 2-, 3- and 5-hydroxy groups, with the anion of a bis (hydrocarbylthio) methane compound, in which the hydrocarbyl group is an alkyl group having 1-6 carbon atoms, a phenyl group or a benzyl group, to form, after hydrolysis of the sulfate group, a 2-deoxy-D-arabino-hexose bis (hydrocarbyl-thio) acetal compound having protected 3-, 4- and 6-hydroxy groups, followed by removal of the dithioacetal group to form a 2-deoxy-α/β-D-arabino-hexopyranose compound having protected 3-, 4- and 6-hydroxy groups, and optionally removing the hydroxy protecting groups or replacing them by other hydroxy protecting groups. In a preferred embodiment, this process for preparing a 2-deoxy-α/β-D-arabino-hexopyranose compound comprises reacting 1,4 cyclic sulfate of 2,3,5-tri-O-benzyl-D-arabinitol of formula 27 with the anion of bis (methylthio) methane to form, after hydrolysis of the sulfate group, 3,4,6-tri-O-benzyl-2-deoxy-D-arabino-hexose bis (methylthio) acetal

of formula 36, followed by removal of the dithioacetal group to form 3,4,6-tri-O-benzyl-2-deoxy-α/β-D-arabino-hexopyranose of formula 40, and optionally removing the hydroxy protecting groups or replacing them by other hydroxy protecting groups.

In general terms, the invention also provides a process for preparing a 2-deoxy-heptono-1,5-lactone compound or a 2-deoxy-hexono-1,5-lactone compound, which process comprises reacting either a 1,4 cyclic sulfate of a D-hexitol having protected 2-, 3-, 5- and 6-hydroxy groups or a 1,4 cyclic sulfate of a D-pentitol having protected 2-, 3- and 5-hydroxy groups, with the anion of a tris (hydrocarbylthio) methane compound, in which the hydrocarbyl group is an alkyl group having 1-6 carbon atoms, a phenyl group or a benzyl group, to form, after hydrolysis of the sulfate group, either a 2-deoxy-heptonic acid hydrocarbylthio orthoacetal compound having protected 3-,4-,6- and 7-hydroxy groups, or a 2-deoxy-hexonic acid hydrocarbylthio orthoacetal compound having protected 3-, 4- and 6-hydroxy groups, followed by removal of the dithio-acetal group to form a 2-deoxy-heptono-1,5-lactone compound having protected 3-,4-,6- and 7-hydroxy groups or a 2-deoxy-hexono-1,5-lactone compound having protected 3-, 4- and 6-hydroxy groups, and optionally removing the hydroxy protecting groups or replacing them by other hydroxy protecting groups.

A more specific example of such a process consists of a process for preparing a 2-deoxy-D-arabino-hexono-1,5-lactone compound, which process comprises reacting a 1,4 cyclic sulfate of a D-arabinitol having protected 2-, 3- and 5-

hydroxy groups, with the anion of a tris (hydrocarbylthio) methane compound, in which the hydrocarbyl group is an alkyl group having 1-6 carbon atoms, a phenyl group or a benzyl group, to form, after hydrolysis of the sulfate group, a 2-deoxy-D-arabino-hexonic acid hydrocarbylthio orthoacetal compound having protected 3-, 4- and 6-hydroxy groups, followed by removal of the dithioacetal group to form a 2-deoxy-D-arabino-hexono-1,5-lactone compound having protected 3-, 4- and 6-hydroxy groups, and optionally removing the hydroxy protecting groups or replacing them by other hydroxy protecting groups. In a preferred embodiment, said process for preparing a 2-deoxy-D-arabino-hexono-1,5-lactone compound comprises reacting 1,4 cyclic sulfate of 2,3,5-tri-O-benzyl-D-arabinitol of formula 27 with the anion of tris (methylthio) methane to form, after hydrolysis of the sulfate group, 3,4,6-tri-O-benzyl-2-deoxy-D-arabino-hexonic acid methylthio orthoacetal of formula 38, followed by removal of the dithioacetal group to form 3,4,6-tri-O-benzyl-2-deoxy-D-arabino-hexono-1,5-lactone of formula 41, and optionally removing the hydroxy protecting groups or replacing them by other hydroxy protecting groups.

The compounds of formula 15 shown in reaction scheme E, such as methyl 3-deoxy-4,5:7,8-di-O-isopropylidene-D-manno-octulonate diethyl dithioacetal, and more in general compounds of formula 22, i.e. 3-deoxy-octulonate dithioacetal compounds having protected 4-,5-,7- and 8-hydroxy groups, are novel compounds which are valuable as allround intermediate

products. Via a cyclisation of these compounds promoted by iodonium ions the KDO glycosyl donors of formula 16 (or more in general formula 23) and formula 17 can be obtained, as shown by reaction schemes F and G, respectively. Reaction schemes H and I show how to use these glycosyl donors of KDO. By glycosidation of a compound of formula 17, in which R is an ester group and R^1-R^4 stand for hydroxy-protecting groups, such as isopropylidene and benzyl groups, with 3-benzyloxycarbonyl-amino-1-propanol of formula 18 (Z is a benzyloxycarbonyl group) in the presence of the in situ prepared thiophilic promoter phenylselenyl triphlate it is possible to obtain only the α-linked glycoside of formula 19, in which R^5 is a -SePh group or a hydrogen atom (the -SePh group can be removed by treatment at elevated temperature with tributyl stannate and azoisobutyronitrile in toluene). By treating a compound of formula 16 with bromine and coupling the glycosyl bromide formed in situ with 3-benzyloxycarbonylamino-1-propanol of formula 18 in the presence of the insoluble halophilic promoter silver silicate aluminate it is possible to obtain the β-linked glycoside of formula 20 after purification on silica gel.

Similarly, 3-deoxy-heptulonate dithioacetal compounds having protected 4-, 5- and 7-hydroxy groups, such as the compounds of formulae 34, 36 and 38, are also potentially useful as intermediates and are comprised by the invention.

The invention will now be elucidated by means of examples. The examples are only for the purpose of elucidation

and illustration of the invention, so the invention is in no way limited by the examples.

EXAMPLES

Preparation 1

Ethyl 1,3-dithiane-2-carboxylate (formula 8, R= ethyl)

A solution of 1,3-propanedithiol (10.8 g, 100 mmol) and ethyl diethoxyacetate (17.6 g, 100 mmol) in dichloromethane (20 ml) was added dropwise to a refluxing solution of BF_3 etherate (28.2 g, 200 mmol) in dichloromethane (60 ml). After refluxing for half an hour the solution was washed with water (80 ml), an aqueous solution of potassium carbonate (80 ml, 20%) and twice with water (80 ml). The organic layer was dried on $MgSO_4$ and evaporated. After distillation (95-97°C, 04 mm) the yield was 65%.

^1H NMR ($CDCl_3$): 1.30 (t, CH_3), 2.10 (m, $SCH_2\underline{CH_2}CH_2S$), 2.60, 3.42 (2xm, $\underline{SCH_2}$), 4.12 (s, CH), 4.22 (q, OCH_2).

$^{13}C\{^1H\}$NMR($CDCl_3$): 13.8 (CH_3), 24.8 (CH_2, $SCH_2\underline{CH_2}CH_2S$), 25.7 (2x$CH_2$, $\underline{SCH_2}$), 39.8 (CH), 61.4 (CH_2, ethyl), 169.5 (C=O).

Preparation 2

Methyl 1,3-dithiane-2-carboxylate (formula 8, R= methyl)

Ethyl 1,3-dithiane-2-carboxylate (192 mg, 1 mmol) was added to a solution of potassium tert. butylate (60 mg, 0.5 mmol) in methanol (10 ml). After stirring for 4 hours the solution was neutralized with Dowex 50W cation exchanger (100-

200 mesh, H^+ form), filtered and evaporated. The yield was 65%.

^1H NMR ($CDCl_3$): 2.10 (m, $SCH_2\underline{CH_2}CH_2S$), 2.61, 3.41 (2xm, $\underline{SCH_2}$), 3.78 (s, OCH_3), 4.20 (s, CH).

$^{13}C\{^1H\}$NMR($CDCl_3$): 24.8 (CH_2, $SCH_2\underline{CH_2}CH_2S$), 25.8 ($2xCH_2$, $\underline{SCH_2}$), 39.6 (CH), 52.4 (OCH_3), 170.0 (C=O).

Preparation 3

Benzyl 1,3-dithiane-2-carboxylate (formula 8, R= benzyl)

Ethyl 1,3-dithiane-2-carboxylate (192 mg, 1 mmol) was added to a solution of potassium tert.butylate (60 mg, 0.5 mmol) in benzyl alcohol (10 ml). After stirring for 4 hours the solution was neutralized with Dowex 50W cation exchanger (100-200 mesh, H^+ form), filtered and evaporated. The resulting oil was evaporated thrice with water and twice with toluene. The oil was brought on a silica gel column (3 gram), suspended in dichloromethane, and the column was eluted with dichloromethane. The right fractions were collected and evaporated. The compound was obtained as a solid in a yield of 70%.

Melting point: 77-78°C (abs. alcohol).

^1H NMR ($CDCl_3$): 2.10 (m, $SCH_2\underline{CH_2}CH_2S$), 2.60, 3.40 (2xm, $\underline{SCH_2}$), 4.20 (s, CH), 5.20 (q, CH_2 benzyl), 7.20 (m, 5 arom H)

$^{13}C\{^1H\}$NMR($CDCl_3$): 24.8 (CH_2, $SCH_2\underline{CH_2}CH_2S$), 25.7 ($2xCH_2$, $\underline{SCH_2}$), 39.6 (CH), 67.1 (CH_2, CH_2 benzyl), 128.0-128.5 (CH, arom benzyl), 169.7 (C=O).

Preparation 4

2,3:5,6-di-isopropylidene-D-mannitol (formula 9)

2,3:5,6-di-isopropylidene-D-manno-furanose (10 g, 38.6 mmol) was dissolved in ethanol (200 ml). Sodium borohydride (1.46 g, 38.6 mmol) was added. After stirring for 1 hour at room temperature TLC analysis (methanol/dichloromethane, 3/97, v/v) showed that the reaction was complete. The pH was brought to 6 with acetic acid and the reaction mixture was evaporated to a small volume and incorporated in dichloromethane (400 ml), washed with an aqueous solution of ammonium chloride (75 ml, 20%), an aqueous solution of sodium bicarbonate (75 ml, 10%) and water (75 ml). The organic layer was dried on magnesium sulfate and evaporated to a colourless oil (compound of formula 9). The yield without purification was 95%.

$^{13}C\{^{1}H\}$NMR($CDCl_3$): 25.3, 25.7, 27.2, 27.2 ($4xCH_3$, isoprop.), 61.1 (C6), 67.7 (C1), 70.8, 76.2, 76.4, 77.5 (C2, C3, C4 and C5), 108.8, 109.9 ($2xC_q$, isoprop.)

Example 1

2,3:5,6-di-isopropylidene-D-mannitol 1,4 cyclic sulfate (formula 2)

To a solution of the compound of formula 9 (2.62 g, 10 mmol) in dichloromethane (30 ml) and triethylamine (5.6 ml, 40 mmol, M=101, d=0.726) was dropped at -15°C a solution of thionyl chloride (1.09 ml, 15 mmol, M=119, d=1.63) in dichloromethane (2.5 ml). After 15 minutes TLC analysis

(acetone/dichloromethane, 3/97, v/v) showed that the reaction was complete. The reaction mixture was taken up in dichloromethane (100 ml), washed with water (30 ml) and twice with an aqueous solution of sodium chloride (30 ml, saturated). The organic layer was dried on magnesium sulfate and evaporated to an oil. The oil was brought on a silica gel (60 g) column, suspended in dichloromethane and the column was eluted with acetone/dichloromethane (0/1 to 3/97, v/v).

The light-coloured oil was dissolved in a mixture of dichloromethane (30 ml) and acetonitrile (30 ml). To this was added water (45 ml), sodium periodate (4.28 g, M=214, 20 mmol) and $RuCl_3.xH_2O$ (12 mg, 35-42% Ru). After 45 minutes TLC analysis (acetone/dichloromethane, 3/97, v/v) showed that the reaction was complete. The reaction mixture was taken up in dichloromethane (100 ml), washed with an aqueous solution of sodium chloride (30 ml, saturated), dried on magnesium sulfate and evaporated. The oil was brought on a silica gel (60 g) column, suspended in dichloromethane, and the column was eluted with acetone/dichloromethane (0/1 to 3/97, v/v). The compound of formula 2 was obtained as a solid in a yield of 85%.

$^{13}C\{^1H\}NMR(CDCl_3)$: 24.7, 24.8, 26.5, 26.8 ($4xCH_3$, isoprop.), 66.2, 68.0 (C1 and C6), 72.9, 73.2, 73.8, 79.4 (C2, C3, C4 and C5), 109.6, 110.2 ($2xC_q$, isoprop.).

Example 2

Ethyl 2,2-(1,3-propyldithio)-2,3-dideoxy-4,5:7,8-di-O-isopropylidene-D-manno-octonate (Formula 12)

Ethyl 1,3-dithiane-2-carboxylate (250 mg, 1.3 mmol) was coevaporated with toluene and dissolved in tetrahydrofuran (2.6 ml) and hexamethylphosphortriamide (0.8 ml). This solution was cooled to -70°C, after which a solution of butyl lithium (0.81 ml, 1.3 mmol, 1.6 M) in hexane was added dropwise. After stirring for 15 minutes the compound of formula 2 (324 mg, 1 mmol) was added in as little tetrahydrofuran as possible. The reaction mixture was then stirred at room temperature. After 1.5 hours concentrated sulphuric acid (50µl) and water (18µl) were added and heated at 50°C for 2 hours.

The reaction mixture was taken up in 20 ml dichloromethane, washed with an aqueous solution of sodium bicarbonate (5 ml, 10%) and water (5 ml). The organic layer was dried on magnesium sulfate and evaporated. The oil was brought on a silica gel (6 g) column, suspended in dichloromethane, and the column was eluted with acetone/dichloromethane (0/1 to 3/97, v/v). The compound of formula 12 was obtained as an oil in a yield of 82%.

$^{13}C\{^{1}H\}$NMR($CDCl_3$): 13.9 (CH_3, Et), 24.2 (CH_2, $SCH_2\underline{CH_2}CH_2S$), 24.3, 25.1, 26.4, 26.6 (4x CH_3, isoprop.), 27.5, 27.6 (2xCH_2, $S\underline{CH_2}CH_2\underline{CH_2}S$), 38.7 (C3), 51.4 (C2), 61.7 (CH_2, Et), 66.8 (C8), 70.5, 73.1, 75.9, 76.1 (C4, C5, C6 and C7), 107.5, 109.0 (2xC_q, isoprop.), 170.4 (C1).

Example 3

Ethyl 4,5:7,8-di-O-isopropylidene-3-deoxy-α(β)D-manno-2-octulosonate (formula 13)

The compound of formula 12 (436 mg, 1 mmol) was dissolved in a mixture of acetonitrile (8 ml) and tetraethylammonium bicarbonate (2 ml, 0.25 M). At 0°C N-bromosuccinimide (5 eq., 0.9 g, M=180) was added. After stirring for 5 minutes the reaction mixture was poured into an aqueous mixture of sodium bicarbonate and sodium sulphite (10 ml, 1/1, w/w, 10%). This mixture was extracted with dichloromethane (20 ml), washed with water (5 ml), dried on magnesium sulfate and evaporated. The oil was brought on a silica gel (6 g) column, suspended in dichloromethane, and the column was eluted with acetone/dichloromethane (0/1 to 3/97, v/v). The compound of formula 13 was obtained as an oil in a yield of 70%.

$^{13}C\{^{1}H\}$NMR ($CDCl_3$): 13.9, 14.0 (2x CH_3, Et), 24 - 27 (8x CH_3, isoprop.), 30.9, 32.3 (2x C3), 61.8, 62.1 (2x CH_2, Et), 66.7, 67.0 (2x C8), 69 - 74 (2x C4, C5, C6 and C7), 94.3, 95.4 (2x C2), 109 - 110 (4x C_q, isoprop.), 169.3, 169.5 (2x C1).

Example 4

Ethyl 3-deoxy-α(β)-D-manno-2-octulosonate and other forms of KDO

Acidolysis ($HOAc/H_2O$) of the isopropylidene groups in the compound of formula 13 resulted in the title compound.

By basic hydrolysis (0.1 N NaOH) of this ethyl ester KDO was obtained in the form of the free acid, after which an

isolation in the form of a crystalline ammonium salt was carried out: melting point 120-122°C: $[\alpha]_D^{20}$ +38.7° (c 1, H_2O); according to the literature melting point 121-124°C; $[\alpha]D^{20}$ +40.3° (c 1.9, H_2O). The ^1H- AND ^{13}C-n.m.r. data of the ethyl ester and of the ammonium salt of KDO fully corresponded to the proposed structures and were in proper accordance with literature data.

By using instead of ethyl 1,3-dithiane-2-carboxylate of formula 3 the corresponding methyl and benzyl esters as starting material the methyl and benzyl esters of KDO were obtained quite analogously in excellent yield.

Preparation 5

Methyl 2,2-bis(ethylthio)acetate (formula 14, R= methyl)

At 0°C and with vigorous stirring 1.29 g (10 mmol) of dichloroacetic acid was added to a suspension of 1.9 g (40 mmol) 50% NaH dispersion in 100 mml tetrahydrofuran (THF). Then 1.86 g (30 mmol) ethanethiol (EtSH) was added slowly to the suspension. The resulting thick reaction mixture was stirred overnight at 25°C. Sufficient water was added to the mixture to dissolve the salts, after which the THF was removed under reduced pressure. The aqueous phase was extracted with 2 x 25 ml hexane and was then acidified with 2N HCl. The milky mixture was extracted with 4 x 50 ml ethyl acetate (EtOAc), the organic layer was dried over anhydrous $MgSO_4$, and the solvent was evaporated. Thus 1.71 g (95%) bis(ethylthio)acetic acid was obtained as a pale yellow liquid.

$^{13}C\{^{1}H\}$NMR ($CDCl_3$): 174.8 (C=O), 49.4 (CH), 24.6 ($S\underline{CH_2}$), 13.6 (CH_3).

To a cooled (-10°C) solution of bis(ethylthio)acetic acid (7.2 g, 40 mmol) in methanol (30 ml) was added 3.2 ml thionyl chloride. After stirring for 1 hour the reaction mixture was refluxed for 30 minutes and concentrated. The residue was coevaporated twice with toluene. Purification by chromatography on silica gel with 1 : 2 diethylether-petroleum ether 40-60 gave the title compound $(EtS)_2CHCOOMe$ in a yield of 7.29 g (93%).

$^{13}C\{^{1}H\}$NMR ($CDCl_3$): 169.7 (C=O), 52.6 (OMe), 49.4 (CH), 24.9 (CH_2), 13.9 (CH_3).

Example 5

Methyl 4,5:7,8-di-O-isopropylidene-3-deoxy-D-manno-octulonate diethyl dithioacetal (formula 15, R= methyl)

To a cooled (-70°C) solution of methyl 2,2-bis(ethylthio) acetate (250 mg, 1.3 mmol) in THF (2.6 ml) and hexamethylphosphortriamide (HMPA, 0.8 ml) was added butyl lithium (0.81 ml, 1.3 mmol, 1.6 M) in hexane. After stirring for 1 hour at -40°C, 2,3:5,6-di-O-isopropylidene-1,4 cyclic sulfate (324 mg, 1 mmol) in 1.5 ml THF was added. After stirring for 20 hours concentrated sulphuric acid (50µl) and water (18µl) were added and the reaction mixture was stirred for 2 hours at 50°C. The reaction mixture was diluted with EtOAc (20 ml), extracted with aq. $NaHCO_3$(5 ml) and H_2O (2 x 5 ml), dried ($MgSO_4$) and concentrated. The residue was chromatographed on

silica gel with 1 : 1 ether-petroleum ether 40-60 to give pure methyl 4,5:7,8-di-O-isopropylidene-3-deoxy-D-manno-octulonate diethyl dithioacetal (329 mg, 75%)

$[\alpha]_D$ -67.2° (c 1); Rf 0.41 in 97:3 dichloromethane acetone

$^{13}C\{^1H\}$NMR ($CDCl_3$): 170.9 (C=O), 109.2, 107.7 (2x Me_2C), 76.2, 76.0, 73.8, 70.8 (C4, C5, C6, C7), 67.0 (C8), 64.3 ($\{EtS\}_2C$), 52.7 (OMe), 37.0 (C3), 26.7, 26.5, 26.2, 24.5 (4x Me_2C), 24.0, 23.5 (2x CH_2S), 13.3 (SCH_2CH_3).

Example 6

Methyl (ethyl-4,5:7,8-di-O-isopropylidene-3-deoxy-2-thio-α-D-manno-2-octulopyranosid)onate (formula 16, R= methyl, R1+R2= R3+R4= isopropylidene)

To a solution of methyl 4,5:7,8-di-O-isopropylidene-3-deoxy-D-manno-octulonate diethyl dithioacetal (438 mg, 1 mmol) and molecular sieve 4A (1 g) in 10 ml 1,2-dichloroethane was added 225 mg N-iodosuccinimide (NIS). After stirring for 20 minutes at 0°C, TLC analysis (acetone/dichloromethane 3:97) showed a full conversion of the compound of formula 15. After work-up and purification by filtration, dilution with dichloromethane, washing with 10% aqueous sodium thiosulfate and water, drying the organic layer ($MgSO_4$), concentrating and column chromatography (silica gel, Merck, 0.063-0.2 mm, 5 g, eluent dichloromethane/acetone 97:3) the title compound (formula 16, R=methyl, $R^1+R^2=R^3+R^4$=isopropylidene) was obtained (77%), together with 5% of methyl 4,5:7,8-di-O-isopropylidene-

2,6-anhydro-2,3-dideoxy-D-manno-2-octenoate (formula 17, R= methyl, $R^1+R^2= R^3+R^4=$ isopropylidene).

^{1}H-NMR (300 MHz, $CDCl_3$): 3.00 (dd, 1 H, $J_{3a,3e}$= 15.3 Hz, H-3e), 1.62 (dd, 1 H, H-3a).

^{13}C-NMR (50 MHz, $CDCl_3$): 83.5 (C2), 32.6 (C3)

Example 7

Methyl 4,5:7,8-di-O-isopropylidene-2,6-anhydro-2,3-dideoxy-D-manno-2-octenoate (formula 17, R= methyl, R1+R2= R3=R4= isopropylidene)

To a solution of methyl 4,5:7,8-di-O-isopropylidene-3-deoxy-D-manno-2-octulonate diethyl dithioacetal (438 mg, 1 mmol) and molecular sieve 4A (1 g) in 5 ml 1,2-dichloroethane was added 938 mg iodonium sym-dicollidine perchlorate (IDCP). After stirring for 1.5 hours at 20°C, TLC analysis (acetone/ dichloromethane 3:97) showed a full conversion of the compound of formula 15 in a single product with Rf 0.52. After work-up and purification by filtration, dilution with dichloromethane, washing with 10% aqueous sodium thiosulfate and water, drying the organig layer ($MgSO_4$), concentrating and column chromatography (silica gel, Merck, 0.063-0.2 mm, 5 g, eluent dichloromethane/acetone 97:3) the title compound (formula 17, R=methyl, $R^1+R^2=R^3+R^4=$isopropylidene) was obtained as a colourless oil (282 mg, 90%, α^{20}D +27.9° {c 1, $CHCl_3$}).

^{1}H-NMR (300 MHz, $CDCl_3$): 6.00 (dd, 1 H, $J_{3,4}$= 3.2 Hz, $^4J_{3,5}$= 1.3 Hz, H-3).

^{13}C-NMR (50 MHz, $CDCl_3$): 143.6 (C2), 110.3 (C3)

Example 8

Methyl (ethyl-4,5,7,8-tetra-O-benzoyl-3-deoxy-2-thio-α-D-manno-2-octulopyranosid)onate (formula 16, R= methyl, R1-R4= benzoyl)

Methyl (ethyl-4,5:7,8-di-O-isopropylidene-3-deoxy-2-thio-α-D-manno-2-octulopyranosid)onate (376 mg, 1 mmol) was dissolved in 4:1 acetic acid-water (10 ml) and stirred for 5 hours at 50°C. The reaction mixture was concentrated and coevaporated with 2 x 10 ml toluene. The residue was dissolved in 10 ml pyridine and benzoyl chloride (0.94 ml, 2 eq.) was added. After stirring for 2 hours aq. $NaHCO_3$ (1 ml, 10%) was added and the reaction mixture was concentrated. The residue was dissolved again in dichloromethane, extracted with aq. $NaHCO_3$, dried ($MgSO_4$) and concentrated. The remaining oil was purified by silica gel chromatography with dichloromethane-acetone (97 : 3) to give the title compound (63%).

$[\alpha]^{20}D$ +17.8° (c 1); Rf 0.62 in 97:3 dichloromethane-acetone.

^1H-NMR ($CDCl_3$): 6.0-5.8 (m, 3 H, H-4, H-5, H-7), 5.0 (dd, 1 H, $J_{5,6}$ ~1, $J_{6,7}$ ~9.2, H-6), 4.88 (dd, 1 H, $J_{7,8a}$ ~2.4, $J_{8a,8b}$ ~12.3, H-8a), 4.68 (dd, 1 H, $J_{7,8b}$ ~3.8, H-8b), 2.6 (m, 4 H, H-3a, H-3e, SCH_2), 1.03 (t, 3 H, SCH_2CH_3).

$^{13}C\{^1H\}$NMR ($CDCl_3$): 168.5 (C1), 85.1 (C2), 69.1, 68.2, 67.8, 65.1 (C4, C5, C6, C7), 62.8 (C8), 52.8 (OMe), 32.3 (C3), 22.7 CH_2S), 13.4 (SCH_2CH_3).

Example 9

Methyl 4,5-O-isopropylidene-7,8-di-O-benzoyl-2,6-anhydro-2,3-dideoxy-D-manno-2-octenoate (formula 17, R= methyl, R1+R2= isopropylidene, R3= R4= benzoyl) and methyl 4,5,7,8-tetra-O-benzoyl-2,6-anhydro-2,3-dideoxy-D-manno-2-octenoate (formula 17, R= methyl, R1= R2= R3= R4= benzoyl)

a) Methyl 4,5-O-isopropylidene-2,6-anhydro-2,3-dideoxy-D-manno-2-octenoate (formula 17, R= methyl, $R^1+R^2=$ isopropylidene, $R^3= R^4=$ H)

314 mg (1 mmol) of the compound methyl 4,5:7,8-di-O-isopropylidene-2,6-anhydro-2,3-dideoxy-D-manno-2-octenoate (formula 17, R= methyl, $R^1+R^2= R^3+R^4=$ isopropylidene) were dissolved in a 4 : 1 mixture of acetic acid-water (10 ml) and stirred for 12 hours. The reaction mixture was concentrated and coevaporated with 2 x 10 ml toluene. The residue was purified by silica gel chromatography with 95:5 dichloro-methane-methanol (81%).

$[\alpha]^{20}D$ +44.5° (c 1); Rf 0.59 in 95:5 dichloromethane-methanol.

$^{13}C\{^1H\}$NMR ($CDCl_3$): 162.1 (C1), 143.6 (C2), 110.9 (Me_2C), 110.4 (C3), 76.0, 71.0, 70.3, 68.9 (C4, C5, C6, C7), 63.4 (C8), 52.4 (OMe), 28.0, 26.6 (Me_2C).

b) Methyl 4,5-O-isopropylidene-7,8-di-O-benzoyl-2,6-anhydro-2,3-dideoxy-D-manno-2-octenoate (formula 17, R= methyl, $R^1+R^2=$ isopropylidene, $R^3= R^4=$ benzoyl).

The compound obtained under a) (274 mg, 1 mmol) was coevaporated and dissolved in 10 ml pyridine. To this solution benzoyl chloride (0.3 ml, 1.3 eq.) was added. After 2 hours 1

ml water was added and the reaction mixture was concentrated. The residue was again dissolved in dichloromethane, extracted with aq. $NaHCO_3$, dried ($MgSO_4$) and concentrated. Chromatography on silica gel with 97:3 dichloromethane-acetone gave the title compound (96%).

$[\alpha]^{20}D$ -34.5° (c 1); Rf 0.64 in 97:3 dichloromethane-acetone.

^1H-NMR ($CDCl_3$): 6.03 (dd, 1 H, $J_{3,4}$ ~3.2, $J_{3,5}$~1.3, H-3), 5.84 (dq, 1 H, $J_{6,7}$ ~7.0, $J_{7,8a}$ ~2.5, $J_{7,8b}$ ~5.9, H-7), 5.03 (dd, 1 H, $J_{8a,8b}$ ~12.3, H-8a), 4.83 (dd, 1 H, $J_{3,4}$ ~3.2, $J_{4,5}$ ~6, H-4), 4.82 (dd, 1 H, H-8b), 4.48 (dt, 1 H, $J_{5,6}$ ~1.3, H-5), 4.41 (dd, 1 H, H-6), 3.78 (s, 3H, OCH_3).

$^{13}C\{^1H\}$NMR ($CDCl_3$): 161.7 (C1), 143.7 (C2), 111.3 (Me_2C), 110.2 (C3), 74.3, 70.9, 68.7 (C4, C5, C6, C7), 62.8 (C8), 52.3 (OMe), 27.9, 26.4 (Me_2C).

c) Methyl 4,5,7,8-tetra-O-benzoyl-2,6-anhydro-2,3-dideoxy-D-manno-2-octenoate (formula 17, R= methyl, R^1= R^2= R^3= R^4= benzoyl).

The procedure of a) and b) was now repeated in one reaction vessel, with 4:1 acetic acid for 5 hours at 50°C, followed by benzoyl chloride in pyridine. The yield was 71%.

$[\alpha]^{20}D$ -156.0° (c 1); Rf 0.73 in 97:3 dichloromethane-acetone.

^1H-NMR ($CDCl_3$): 6.12 (m, 2 H, H-3, H-4), 5.99 (m, 1 H, H-5), 5.82 (dq, 1 H, $J_{6,7}$ ~9.3, $J_{7,8a}$ ~2.5, $J_{7,8b}$ ~4.6, H-7), 4.96 (dd, 1 H, $J_{8a,8b}$ ~12.1, H-8a), 4.79 (dd, 1 H, H-6), 4.77 (dd, 1 H, H-8b), 3.79 (s, 3 H, OCH_3).

$^{13}C\{^1H\}$NMR ($CDCl_3$): 160.9 (C1), 144.8 (C2), 107.5 (C3), 74.1, 68.0, 65.4, 61.6 (C4, C5, C6, C7), 61.5 (C8), 52.5 (COOMe).

Example 10

Stereoselective glycosylation of compounds of formula 17

To a mixture of phenylselenyl chloride (0.2 mmol, 77 mg) and molecular sieve 4A (0.2 g) in 2 ml 1,2-dichloroethane was added silver triflate (0.2 mmol, 51 mg) at 0°C. After stirring for 30 minutes a solution of 0.1 mmol of a glycal of formula 17 and 0.12 mmol of 3-benzyloxycarbonylamino-1-propanol in 2 ml 1,2-dichloroethane was added. The mixture was stirred for 1 hour at 0°C, filtered, and the filtrate was washed with aq. $NaHCO_3$, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on silica gel.

In order to selectively remove the phenylselenyl group the resulting compound of formula 19, in which R^5 is a phenylselenyl group, was treated under reflux for 2 hours with 2 equivalents tributyl stannate (n-Bu_3SnH) and a catalytic amount of azoisobutyronitrile (AIBN) in toluene (5 ml/mmol). The mixture was concentrated and the residue was chromatographed on silica gel.

The results were as follows.

a) Methyl (N-benzyloxycarbonyl-3-aminopropyl-3-phenyl-seleno-4,5:7,8-di-O-isopropylidene-3-deoxy-α-D-manno-2-octulo-pyranosid)onate of formula 19, R= methyl, $R^1+R^2= R^3+R^4=$ isopropylidene, $R^5=$ SePh, Z= benzyloxycarbonyl.

Yield 41%; $[\alpha]^{20}D$ +36.8° (c 1); Rf 0.38 in 97:3 dichloro-methane-acetone.

$^{13}C\{^1H\}$NMR ($CDCl_3$): 167.3 (C1), 109.5, 109.3 (Me_2C), 101.4 (C2), 76.8, 74.1, 73.1, 71.6 (C4, C5, C6, C7), 66.4, 66.3,

62.4 ($O\underline{CH_2}CH_2$, $O\underline{CH_2}Ph$, C8), 52.4 (OMe), 49.1 (C3), 38.9 (CH_2NHZ), 28.9 ($CH_2\underline{CH_2}CH_2$), 27.7, 26.8, 25.8, 25.1 (Me_2C).

b) Methyl (N-benzyloxycarbonyl-3-aminopropyl-4,5:7,8-di-O-isopropylidene-3-deoxy-α-D-manno-2-octulopyranosid)onate of formula 19, R= methyl, $R^1+R^2= R^3+R^4=$ isopropylidene, $R^5=$ H, Z= benzyloxycarbonyl.

Yield 78%; $[\alpha]^{20}D$ -62.3° (c 1); Rf 0.17 in 97:3 dichloromethane-acetone.

$^{13}C\{^1H\}$NMR ($CDCl_3$): 170.3 (C1), 109.3, 109.1 (Me_2C), 98.2 (C2), 73.7, 73.6, 71.1, 69.8 (C4, C5, C6, C7), 66.7, 66.2, 62.5 ($O\underline{CH_2}CH_2$, $O\underline{CH_2}Ph$, C8), 52.4 (OMe), 38.7 ($\underline{CH_2}NHZ$), 32.4 (C3), 29.0 ($CH_2\underline{CH_2}CH_2$), 26.9, 26.2, 25.0, 24.6 (Me_2C).

^1H-NMR ($CDCl_3$): 2.31 (dd, 1 H, $J_{3a,3e}$ ~15.6, $J_{3e,4}$ ~3.6, H-3e), 1.98 (dd, 1 H, $J_{3a,4}$ ~3.8, H-3a).

c) Methyl (N-benzyloxycarbonyl-3-aminopropyl-3-phenyl-seleno-4,5-O-isopropylidene-7,8-di-O-benzoyl-3-deoxy-αD-manno-2-octulopyranosid)onate of formula 19, R= methyl, $R^1+R^2=$ isopropylidene, $R^3= R^4=$ benzoyl, $R^5=$ SePh, Z= benzyloxycarbonyl.

Yield 43%; $[\alpha]^{20}D$ +39.3° (c 1); Rf 0.49 in 97:3 dichloromethane-acetone.

$^{13}C\{^1H\}$NMR ($CDCl_3$): 167.8 (C1), 109.4 (Me_2C), 101.5 (C2), 76.9, 71.3, 70.7, 70.4 (C4, C5, C6, C7), 66.2, 62.9, 62.6 ($O\underline{CH_2}CH_2$, $O\underline{CH_2}Ph$, C8), 52.2 (OMe), 49.9 (C3), 39.1 (CH_2NHZ), 28.9 ($CH_2\underline{CH_2}CH_2$), 27.7, 25.7, (Me_2C).

d) Methyl (N-benzyloxycarbonyl-3-aminopropyl-4,5-O-isopropylidene-7,8-di-O-benzoyl-3-deoxy-α-D-manno-2-

octulopyranosid)onate of formula 19, R= methyl, R^1+R^2= isopropylidene, R^3= R^4= benzoyl, R^5= H, Z= benzyloxycarbonyl.

Yield 79%; $[\alpha]^{20}D$ -1.5° (c 1); Rf 0.23 in 97:3 dichloromethane-acetone.

$^{13}C\{^1H\}$NMR ($CDCl_3$): 169.3 (C1), 109.3 (Me_2C), 98.3 (C2), 71.2, 70.8, 70.6, 70.0 (C4, C5, C6, C7), 66.1, 63.3, 62.7 ($O\underline{CH_2}CH_2$, $O\underline{CH_2}Ph$, C8), 38.8 ($\underline{CH_2}NHZ$), 32.8 (C3), 29.1 ($CH_2\underline{CH_2}CH_2$), 26.5, 24.7 (Me_2C).

^1H-NMR ($CDCl_3$): 2.25 (dd, 1 H, $J_{3a,3e}$ ~15.1, $J_{3e,4}$ ~4.6, H-3e), 2.10 (dd, 1 H, $J_{3a,4}$ ~4.3, H-3a).

e) Methyl (N-benzyloxycarbonyl-3-aminopropyl-3-phenylseleno-4,5,7,8-tetra-O-benzoyl-3-deoxy-α-D-manno-2-octulopyranosid)onate of formula 19, R= methyl, R^1= R^2= R^3= R^4= benzoyl, R^5= SePh, Z= benzyloxycarbonyl.

Yield 85%; $[\alpha]^{20}D$ +14.7° (c 1); Rf 0.62 in 97:3 dichloromethane-acetone.

$^{13}C\{^1H\}$NMR ($CDCl_3$): 167.8 (C1), 102.4 (C2), 68.6, 68.2, 67.3, 64.9 (C4, C5, C6, C7), 66.5, 62.8, 61.8 ($O\underline{CH_2}CH_2$, $O\underline{CH_2}Ph$, C8), 51.9 (OMe), 47.4 (C3), 37.9 (CH_2NHZ), 28.9 ($CH_2\underline{CH_2}CH_2$).

f) Methyl (N-benzyloxycarbonyl-3-aminopropyl-4,5,7,8-tetra-O-benzoyl-3-deoxy-α-D-manno-2-octulopyranosid)onate of formula 19, R= methyl, R^1= R^2= R^3= R^4= benzoyl, R^5= H, Z= benzyloxycarbonyl.

Yield 80%; $[\alpha]^{20}D$ -31.4° (c 1); Rf 0.62 in 97:3 dichloromethane-acetone.

$^{13}C\{^{1}H\}$NMR ($CDCl_3$): 169.4 (C1), 99.2 (C2), 69.2, 68.4, 67.3, 65.2 (C4, C5, C6, C7), 66.5, 62.9, 61.7 ($O\underline{CH_2}CH_2$, $O\underline{CH_2}Ph$, C8), 51.9 (OMe), 37.9 ($\underline{CH_2}NHZ$), 32.6 (C3), 29.1 ($CH_2\underline{CH_2}CH_2$).
^{1}H-NMR ($CDCl_3$): 2.41 (dd, 1 H, $J_{3a,3e}$ ~12.6, $J_{3e,4}$ ~6.0, H-3e), 2.35 (t, 1 H, H-3a).

Example 11

Stereoselective glycosylation of a compound of formula 16

To a cooled (0°C) solution of the compound methyl(ethyl-4,5,7,8-tetra-O-benzoyl-3-deoxy-2-thio-α-D-manno-2-octulo-pyranosid)onate of formula 16, in which R= methyl and R^1 to R^4= benzoyl (142 mg, 0.2 mmol) in 1.5 ml 1,2-dichloroethane and molecular sieve 4A was added Br_2 (1.3 eq., 0.013 ml). After 10 minutes at 0°C the reaction mixture was concentrated. The remaining bromide was added to a mixture of N-benzyloxy-carbonyl-3-aminopropanol (50 mg, 1.2 eq.), molecular sieve 4A (200 mg), silver silicate (200 mg) in 2 ml 1,2 dichloromethane at -40°C. After stirring for 3 hours at room temperature the mixture was filtered and concentrated. The residue was chromatographed on silica gel with 97:3 dichloromethane-acetone to give the compound methyl ((N-benzyloxycarbonyl-3-aminopropyl-4,5,7,8-tetra-O-benzoyl-3-deoxy-β-D-manno-2-octulopyranosid)onate of formula 20 (60%).
$[\alpha]^{20}D$ -23.1° (c 1); Rf 0.62 in 97:3 dichloromethane-acetone.
$^{13}C\{^{1}H\}$NMR ($CDCl_3$): 168.4 (C1), 99.4 (C2), 71.5, 68.6, 67.9, 64.7 (C4, C5, C6, C7), 66.4, 62.9, 62.4 (CH_2 of benzyl, C1 of

spacer, C8), 52.7 (COOMe), 38.3 ($\underline{CH_2}NHZ$), 32.6 (C3), 29.2 ($CH_2\underline{CH_2}CH_2$).

^{1}H-NMR ($CDCl_3$): 2.62 (dd, 1 H, $J_{3a,3e}$ ~12.5, $J_{3e,4}$ ~4.7, H-3e), 2.40 (t, 1 H, H-3a).

Preparation 6

Methyl 2,3,5-tri-O-benzyl-α/β-D-arabinopyranoside (formula 24)

D-arabinose (1.5 g, 10 mmol) was added to a mixture of anhydrous methanol (40 ml) and acetyl chloride (0.71 ml). After stirring for 12 hr at 20°C the mixture was neutralized with sodium methoxide and concentrated. The sirup was dissolved in N,N-dimethylformamide (30 ml) and sodium hydride (1.19 g, 80%, 1.3 equiv.) and benzyl bromide (4.3 ml, 1.3 equiv.) were added. After 2 hr, methanol (10 ml) was added, and the mixture was concentrated, redissolved in dichloromethane (100 ml), extracted with water (20 ml) and brine (20 ml), dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel [eluent petroleum ether (40-60°C)/diethyl ether; 1 : 1] to give the title compound of formula 24.

Yield: 3.6 g (83%); Rf 0.75 [A, i.e. petroleum ether (40-60°C)/diethyl ether 1/1]; $[\alpha]^{20}D$ +24.7° (c 1, chloroform)

$C_{27}H_{30}O_5$	calc.	C 74.6	H 7.0
(434.5)	found	74.4	6.9

$^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 138.3, 138.0, 137.9, 137.7 (C_{arom}), 129-127 (CH_{arom}), 107.3 (C-1, α), 101.7 (C-1, β), 88.3 (C-2, α), 84.5 (C-2, β), 83.6 (C-3, α), 83.4 (C-3, β), 81.0 (C-4, α),

80.4 (C-4, β), 73.3, 72.6, 72.3, 72.1, 72.0, 71.8, 69.9 (C-5, CH_2Ph, α/β), 54.8 (OMe).

Preparation 7

2,3,5-Tri-O-benzyl-D-arabinitol (formule 25)

Methyl 2,3,5-tri-O-benzyl-α/β-D-arabinopyranoside (3.5 g, 8 mmol) was dissolved in 4 : 1 acetic acid : water (50 ml) and heated under reflux for 24 hr. The mixture was concentrated and coevaporated with toluene (3 x 20 ml). The resulting oil and sodium borohydride (0.29 g) were dissolved in ethanol (40 ml), and the mixture was stirred at room temperature for 1 hr. The pH was adjusted to 6 by the addition of acetic acid and the solution was evaporated to dryness. The residue was diluted with dichloromethane (100 ml), washed with water (20 ml), dried ($MgSO_4$) and concentrated. Purification by chromatography on silica gel (eluent dichloromethane/methanol 97 : 3) gave the title compound of formula 25.

Yield: 3.05 g (90%, based on the compound of formula 24); Rf 0.52 (B, i.e. dichloromethane/acetone 95/5); $[\alpha]^{20}D$ +6.8° (c 1, chloroform)

$C_{26}H_{30}O_5$ calc. C 73.9 H 7.2

(422.5) found 74.1 7.0

$^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 137.8, 137.7, 137.6 (C_{arom}), 128-126 (CH_{arom}), 79.3, 78.1, 70.0 (C-2, C-3, C-4), 73.4, 72.9, 72.4, 70.9, 60.8 (CH_2Ph, C-1, C-5).

Voorbeeld 12

2,3,5-Tri-O-benzyl-D-arabinitol 1,4-sulfaat (formule 27)

To a cooled (-15°C) solution of 2,3,5-tri-O-benzyl-D-arabinitol (2.95 g, 7 mmol) and triethylamine (3.9 ml, 4 eq.) in dichloromethane (20 ml) was added thionyl chloride (0.76 ml, 1.5 eq.) in dichloromethane (2 ml). After stirring for 15 min at -15°C the mixture was diluted with dichloromethane (100 ml), washed with water (20 ml) and brine (20 ml), dried ($MgSO_4$) and evaporated. The residue was filtered through a pad of silica gel (eluent dichloromethane/acetone (97 : 3)). The filtrate was evaporated and to a solution of the resulting, coloured oil (compound of formula 26) in dichloromethane (20 ml) and acetonitrile (20 ml) was added water (30 ml), sodium periodate (3 g, 2 eq.) and ruthenium chloride (10 mg) and the mixture was stirred vigorously for 1 hr at room temperature. Dichloromethane (100 ml) was added and the layers were separated. The organic layer was washed with brine (25 ml), dried ($MgSO_4$) and concentrated. The residue was filtered through a pad of silica gel (eluent dichloromethane/acetone 97 : 3) to afford the title compound of formula 27. Yield: 2.84 g (84%); Rf 0.71 (C, i.e. dichloromethane/acetone 97/3); $[\alpha]^{20}D$ +26.9° (c 1, chloroform)

$C_{26}H_{28}O_7$ calc. C 64.5 H 5.8

(484.6) found 64.6 5.8

$^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 137.4, 137.1, 136.9 (C_{arom}), 129-127 (CH_{arom}), 80.9, 79.4, 77.8 (C-2, C-3, C-4), 75.2, 73.5, 73.3 (CH_2Ph), 67.7, 67.5 (C-1, C-5).

Voorbeeld 13

(a) Ethyl 4,5,7-tri-O-benzyl-2,3-dideoxy-D-arabino-heptulonate propylene dithioacetal (formula 34)

Ethyl 2-carboethoxy-1,3-dithiane (1.3 mmol) was dissolved in dry tetrahydrofuran (2.6 ml) and hexamethylphosphoramide (0.8 ml). The temperature was lowered to -60°C and n-butyl-lithium (0.81 ml, 1.6 M) was added. After stirring for 1.5 hr at -40°C 2,3,5-tri-O-benzyl-D-arabinitol 1,4-sulfaat of formula 27 (484 mg, 1 mmol in tetrahydrofuran) was added. The mixture was allowed to warm to room temperature and stirred until TLC-analysis, after 16 hr showed complete conversion of the cyclic sulfate. Now sulfuric acid (50 µl) and water (18 µl) were added and the mixture was stirred for 2 hr at 50°C. The mixture was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate (2 x 5' ml) and water (5 ml), dried ($MgSO_4$) and concentrated. The resulting oil was chromatographed on silica gel [eluent petroleum ether (40-60°C)/ether 1 : 1] to give the title compound of formula 34.

Yield: 357 mg (60%); Rf 0.53 (C); $[\alpha]^{20}D$ +12.8° (c 1, chloroform)

$C_{33}H_{40}O_6S_2$ calc.	C 66.4	H 6.8
(596.8) found	66.6	6.7

$^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 170.5 (C-1), 138.2, 137.6, 137.2 (C_{arom}), 129-127 (CH_{arom}), 75.7, 75.3 (C-4, C-5), 73.4, 73.0, 72.7 (CH_2Ph), 71.2 (C-7), 71.1 (C-6), 61.7 ($\underline{C}H_2CH_3$), 52.9 (C-2), 38.7 (C-3), 27.8, 27.4, 24.6 ($SCH_2CH_2CH_2S$), 13.8 ($CH_2\underline{C}H_3$).

(b) 3,4,6-Tri-O-benzyl-2-deoxy-D-arabino-hexose bis (methylthio) acetal (formula 36)

Following the same procedure, but using the compound $CH_2(SMe)_2$ instead of ethyl 2-carboethoxy-1,3-dithiane, the title compound was obtained in a yield of 54%; Rf 0.75 (C); $[\alpha]^{20}D$ +13.9° (c 1, chloroform)

$C_{29}H_{36}O_4S_2$ calc. C 67.9 H 7.1

(512.7) found 67.7 7.1

$^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 138.1, 137.8 (C_{arom}), 129-126 (CH_{arom}), 76.9, 76.6, 71.0 (C-3, C-4, C-5), 73.5, 73.3, 73.1 (CH_2Ph), 71.2 (C-6), 51.0 (C-1), 35.3 (C-2), 13.1 (CH_3S).

(c) 3,4,6-Tri-O-benzyl-2-deoxy-D-arabino-hexonic acid methylthio orthoacetal (formula 38)

Following the same procedure as under (a), but using the compound $CH(SMe)_3$ instead of ethyl 2-carboethoxy-1,3-dithiane, the title compound was obtained in a yield of 60%; Rf 0.77 (C); $[\alpha]^{20}D$ +11.3° (c 1, chloroform)

$C_{30}H_{38}O_4S_3$ calc. C 64.5 H 6.9

(558.8) found 64.6 6.8

$^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 138.3, 137.6, 137.5 (C_{arom}), 129-127 (CH_{arom}), 77.1, 74.6, 71.7 (C-3, C-4, C-5), 73.5, 72.8, 72.6 (CH_2Ph), 71.3 (C-6), 71.0 (C-1), 37.9 (C-2), 13.0 (CH_3S).

Voorbeeld 14

(a) Ethyl 4,5,7-tri-O-benzyl-3-deoxy-α-D-arabino-heptulo-pyranosoate (formula 39)

To a cooled solution (0°C) of the compound ethyl 4,5,7-tri-O-benzyl-2,3-dideoxy-D-arabino-heptulonate propylene dithioacetal (formula 34; 1 mmol) in a mixture of acetonitrile (8 ml) and aqueous triethylammonium bicarbonate (2 ml, 0.25 M) was added N-bromosuccinimide (4 mmol). After stirring for 5 min, the solution was poured in an aqueous mixture of sodium bicarbonate and sodium thiosulfite (50 ml, 1/1, w/w, 10%) and diluted with dichloromethane (75 ml). The organic phase was washed with water (15 ml), dried ($MgSO_4$) and concentrated. The oil thus obtained was purified by silica gel column chromatography [eluent petroleum ether (40-60°C)/ether (1 : 1)] to afford the title compound of formula 39.

Yield: 435 mg (86%); Rf 0.71 (B); $[\alpha]^{20}D$ +25.4° (c 1, chloroform)

$C_{30}H_{34}O_7$ calc.	C 71.1	H 6.8
(506.6) found	71.3	6.9

^1H NMR ($CDCl_3$): δ 7.5-7.0 (m, $15H_{arom}$), 5.0-4.5 (m, 6H, CH_2Ph), 4.66 (m, 2H, $C\underline{H}_2CH_3$), 4.04 (m, 2H, H-4, H-6), 3.75 (dd, 1H, $J_{6,7}$=4.6, $J_{7,7'}$=11, H-7), 3.66 (dd, 1H, $J_{6,7'}$=1.8, H-7'), 3.61 (dd, 1H, J=9.2, 9.8, H-5), 2.29 (dd, 1H, $J_{3e,3a}$=12, $J_{3e,4}$=5.0, H-3e), 2.10 (t, 1H, $J_{3a,4}$= 12 Hz, H-3a), 1.31 (t, 3H, CH_3CH_2).

$^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 169.8 (C-1), 138.4, 138.2 (C_{arom}), 129-127 (CH_{arom}), 94.8 (C-2), 78.0, 77.5, 73.0 (C-4, C-5, C-6),

74.9, 73.2, 71.7 (CH_2Ph), 68.9 (C-7), 62.4 ($\underline{C}H_2CH_3$), 36.1 (C-3), 13.9 ($CH_2\underline{C}H_3$).

(b) 3,4,6-Tri-O-benzyl-2-deoxy-α/β-D-arabino-hexopyranose (formule 40)

Following the same procedure as under (a), but using the compound 3,4,6-tri-O-benzyl-2-deoxy-D-arabino-hexose bis (methylthio) acetal (formula 36) instead of ethyl 4,5,7-tri-O-benzyl-2,3-dideoxy-D-arabino-heptulonate propylene dithio acetal, the title compound was obtained in a yield of 84%; Rf 0.27 (C); m.p. 97-99°C; $[\alpha]^{20}D$ +48.9° (c 1, chloroform)

$C_{27}H_{30}O_5$ calc.	C 74.6	H 7.0	
(434.5) found	74.6	7.1	

$^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 138.4, 138.3, 137.7 (C_{arom}), 129-127 (CH_{arom}), 94.0 (C-1, β), 91.9 (C-1, α), 79.1, 77.7, 74.7 (C-3, C-4, C-5, β), 78.6, 77.0, 70.6 (C-3, C-4, C-5, α), 74.8, 73.3, 71.7 (CH_2Ph), 71.3 (C-6, β), 69.3 (C-6, α), 37.8 (C-2, β), 35.5 (C-2, α).

(c) 3,4,6-Tri-O-benzyl-2-deoxy-D-arabino-hexono-1,5-lactone (formula 41)

Following the same procedure as under (a), but using the compound 3,4,6-tri-O-benzyl-2-deoxy-D-arabino-hexonic acid methylthio orthoacetal (formula 38) instead of ethyl 4,5,7-tri-O-benzyl-2,3-dideoxy-D-arabino-heptulonate propylene dithio acetal, the title compound was obtained in a yield of 83%; Rf 0.85 (C); m.p. 82-83°C; $[\alpha]^{20}D$ +44.0° (c 1, ethanol)

$C_{27}H_{28}O_5$ calc. C 75.0 H 6.5

(432.5) found 75.0 6.5

^1H NMR ($CDCl_3$): δ 7.5-7.0 (m, $15H_{arom}$), 4.7-4.4 (m, 6H, CH_2Ph), 4.3 (dt, 1H, $J_{4,5}$= 7.3 Hz, $J_{5,6}$= $J_{5,6'}$= 4 Hz, H-5), 3.95 (q, 1H, $J_{2a,3}$= $J_{2e,3}$= $J_{3,4}$= 4.5 Hz, H-3), 3.88 (ddd, 1H, $J_{2a,4}$= 0.6 Hz, H-4), 3.73 (dd, 1H, $J_{6,6'}$= 11.3 Hz, H-6), 3.70 (dd, 1H, H-6'), 2.85 (dd, 1H, $J_{2a,2e}$= 16.4 Hz, H-2e), 2.75 (ddd, 1H, H-2a).

$^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 169.2 (C-1), 137.2 (C_{arom}), 129-127 (CH_{arom}), 79.2, 75.0, 74.6 (C-3, C-4, C-5), 73.4, 72.7, 71.0 (CH_2Ph), 68.7 (C-6), 33.6 (C-2).

CLAIMS

1. A 1,4 cyclic sulfate of a sugar alcohol having protected hydroxy groups.

2. A 1,4 cyclic sulfate according to claim 1, which is a 1,4 cyclic sulfate of a hexitol having protected 2-, 3-, 5- and 6-hydroxy groups, or a 1,4 cyclic sulfate of a pentitol having protected 2-, 3- and 5-hydroxy groups.

3. A 1,4 cyclic sulfate according to claim 1, which is a 1,4 cyclic sulfate of a D-mannitol having protected 2-, 3-, 5- and 6-hydroxy groups, or a 1,4 cyclic sulfate of a D-arabinitol having protected 2-, 3- and 5-hydroxy groups.

4. A 1,4 cyclic sulfate according to claim 1, which is the 1,4 cyclic sulfate of 2,3:5,6-di-O-isopropylidene-D-mannitol of formula 2.

5. A 1,4 cyclic sulfate according to claim 1, which is the 1,4 cyclic sulfate of 2,3,5-tri-O-benzyl-D-arabinitol of formula 27.

6. A process for preparing a 1,4 cyclic sulfate of a sugar alcohol having protected hydroxy groups, in which a sugar alcohol having free 1- and 4-hydroxy groups, its remaining hydroxy groups being protected, is reacted with thionyl chloride in the presence of an acid binding agent and the

resulting 1,4 cyclic sulfite is oxidized to the corresponding 1,4 cyclic sulfate.

7. A process for preparing a 1,4 cyclic sulfate of a hexitol having protected 2-, 3-, 5- and 6-hydroxy groups, or a 1,4 cyclic sulfate of a pentitol having protected 2-, 3- and 5-hydroxy groups, in which a hexitol, the 2-, 3-, 5- and 6-hydroxy groups of which are protected, or a pentitol, the 2-, 3-, and 5-hydroxy groups of which are protected, is reacted with thionyl chloride in the presence of an acid binding agent and the resulting 1,4 cyclic sulfite is oxidized to the corresponding 1,4 cyclic sulfate.

8. A process for preparing a 1,4 cyclic sulfate of a D-mannitol having protected 2-, 3-, 5- and 6-hydroxy groups, or a 1,4 cyclic sulfate of a D-arabinitol having protected 2-, 3- and 5-hydroxy groups, in which a D-mannitol, the 2-, 3-, 5- and 6-hydroxy groups of which are protected, or a D-arabinitol, the 2-, 3-, and 5-hydroxy groups of which are protected, is reacted with thionyl chloride in the presence of an acid binding agent and the resulting 1,4 cyclic sulfite is oxidized to the corresponding 1,4 cyclic sulfate.

9. A process for preparing 1,4 cyclic sulfate of 2,3:5,6-di-O-isopropylidene-D-mannitol of formula 2, in which 2,3:5,6-di-O-isopropylidene-D-mannitol is reacted with thionyl chloride in the presence of an acid binding agent and the resulting 1,4 cyclic sulfite is oxidized to the corresponding 1,4 cyclic sulfate.

10. A process for preparing 1,4 cyclic sulfate of 2,3,5-tri-O-benzyl-D-arabinitol of formula 27, in which 2,3,5-tri-O-benzyl-D-arabinitol is reacted with thionyl chloride in the presence of an acid binding agent and the resulting 1,4 cyclic sulfite is oxidized to the corresponding 1,4 cyclic sulfate.

11. A process for preparing a 3-deoxy-2-octulosonic acid compound or a 3-deoxy-2-heptulosonic acid compound having protected or unprotected hydroxy groups, or a salt or ester thereof, which comprises reacting either a 1,4 cyclic sulfate of a hexitol having protected 2-, 3-, 5- and 6-hydroxy groups or a 1,4 cyclic sulfate of a pentitol having protected 2-, 3- and 5-hydroxy groups, with the anion of a dithioacetal compound of a glyoxylic acid ester, hydrolysing the sulfate group, removing the dithioacetal group, optionally removing the hydroxy protecting groups and optionally converting the resulting ester into the free acid, a salt or another ester of the 3-deoxy-2-octulosonic acid or 3-deoxy-2-heptulosonic acid compound.

12. A process for preparing a 3-deoxy-D-manno-2-octulosonic acid compound of formula 1 having protected or unprotected hydroxy groups, or a salt or ester thereof, which comprises reacting a 1,4 cyclic sulfate of a D-mannitol having protected 2-, 3-, 5- and 6-hydroxy groups with the anion of a dithioacetal compound of a glyoxylic acid ester, hydrolysing the sulfate group, removing the dithioacetal group, optionally removing the hydroxy protecting groups and optionally converting the resulting ester into the free acid, a salt or

another ester of the 3-deoxy-D-manno-2-octulosonic acid compound.

13. A process according to claim 12, in which 1,4 cyclic sulfate of 2,3:5,6-di-O-isopropylidene-D-mannitol of formula 2 is used as the 1,4 cyclic sulfate of a D-mannitol having protected 2-, 3-, 5- and 6-hydroxy groups.

14. A process for preparing a 3-deoxy-D-arabino-2-heptulosonic acid compound of formula 39 having protected or unprotected hydroxy groups, or a salt or ester thereof, which comprises reacting a 1,4 cyclic sulfate of a D-arabinitol having protected 2-, 3- and 5-hydroxy groups with the anion of a dithioacetal compound of a glyoxylic acid ester, hydrolysing the sulfate group, removing the dithioacetal group, optionally removing the hydroxy protecting groups and optionally converting the resulting ester into the free acid, a salt or another ester of the 3-deoxy-D-arabino-2-heptulosonic acid compound.

15. A process according to claim 14, in which 1,4 cyclic sulfate of 2,3,5-tri-O-benzyl-D-arabinitol of formula 27 is used as the 1,4 cyclic sulfate of a D-arabinitol having protected 2-, 3- and 5-hydroxy groups.

16. A process according to any of claims 11-15, in which an anion of a dithioacetal compound of a (C_1-C_4) alkyl or benzyl ester of glyoxylic acid is used as the anion of a dithioacetal compound of a glyoxylic acid ester.

17. A process according to any of claims 11-15, in which an anion of a 1,3-dithiane-2-carboxylic acid ester is used as the anion of a dithioacetal compound of a glyoxylic acid ester.

18. A process according to claim 17, in which the anion of ethyl 1,3-dithiane-2-carboxylate of formula 3 is used as the anion of a dithioacetal compound of a glyoxylic acid ester.

19. A process for preparing a 3-deoxy-2-thio-2-octulosonic acid derivative or a 3-deoxy-2-thio-2-heptulosonic acid derivative, or a salt or ester thereof, in which derivative the hydroxy group attached to the carbon atom at position 2 is replaced by a thio group $-SR^6$, wherein R^6 is an alkyl group having 1-6 carbon atoms, a phenyl group or a benzyl group, in which process either a 1,4 cyclic sulfate of a D-hexitol having protected 2-, 3-, 5- and 6-hydroxy groups or a 1,4 cyclic sulfate of a D-pentitol having protected 2-, 3- and 5-hydroxy groups, is reacted with the anion of a glyoxylic acid ester dithioacetal compound of formula 21, in which R is an ester group and R^6 an alkyl group having 1-6 carbon atoms, a phenyl group or a benzyl group, to form, after hydrolysis of the sulfate group, either a 3-deoxy-octulonate dithioacetal compound having protected 4-,5-,7- and 8-hydroxy groups, or a 3-deoxy-heptulonate dithioacetal compound having protected 4-, 5- and 7-hydroxy groups, which compound is cyclized using iodonium ions to form a 3-deoxy-2-thio-2-octulosonic acid ester having protected hydroxy groups or a 3-deoxy-2-thio-2-heptulosonic acid ester having protected hydroxy groups, optionally removing the hydroxy protecting groups or replacing

them by other hydroxy protecting groups and optionally converting the resulting ester into the free acid, a salt or another ester.

20. A process for preparing a 3-deoxy-D-manno-2-octulosonic acid derivative of formula 23, or a salt or ester thereof, in which R is a hydrogen atom, an ester group or a cation, R^1-R^4 independently of each other stand for hydrogen atoms or hydroxy protecting groups and R^6 is an alkyl group having 1-6 carbon atoms, a phenyl group or a benzyl group, in which a 1,4 cyclic sulfate of a D-mannitol having protected 2-, 3-, 5- and 6-hydroxy groups is reacted with the anion of a glyoxylic acid ester dithioacetal compound of formula 21, in which R is an ester group and R^6 an alkyl group having 1-6 carbon atoms, a phenyl group or a benzyl group, to form, after hydrolysis of the sulfate group, a compound of formula 22, in which R and R^6 have the above meanings and R^1-R^4 are hydroxy protecting groups, which compound of formula 22 is cyclized using iodonium ions to form a compound of formula 23, optionally removing the hydroxy protecting groups or replacing them by other hydroxy protecting groups and optionally converting the resulting ester into the free acid, a salt or another ester.

21. A process according to claim 20, in which 1,4 cyclic sulfate of 2,3:5,6-di-O-isopropylidene-D-mannitol of formula 2 is reacted with a glyoxylic acid ester dithioacetal compound of formula 14, in which R is an ester group, to form a compound of formula 15 which is cyclized by means of N-iodosuccinimide to a compound of formula 16, in which R^1+R^2

and R^3+R^4 are hydroxy protecting isopropylidene groups and R is an ester group, optionally removing the hydroxy protecting groups or replacing them by other hydroxy protecting groups and optionally converting the resulting ester into the free acid, a salt or another ester.

22. A process for preparing a 2,6-anhydro-2,3-dideoxy-2-octenoate compound or a 2,6-anhydro-2,3-dideoxy-2-heptenoate compound, or a salt or ester thereof, in which process either a 1,4 cyclic sulfate of a D-hexitol having protected 2-, 3-, 5- and 6-hydroxy groups or a 1,4 cyclic sulfate of a D-pentitol having protected 2-, 3- and 5-hydroxy groups, is reacted with the anion of a glyoxylic acid ester dithioacetal compound of formula 21, in which R is an ester group and R^6 is an alkyl group having 1-6 carbon atoms, a phenyl group or a benzyl group, to form, after hydrolysis of the sulfate group, either a 3-deoxy-octulonate dithioacetal compound having protected 4-,5-,7- and 8-hydroxy groups, or a 3-deoxy-heptulonate dithioacetal compound having protected 4-, 5- and 7-hydroxy groups, which compound is cyclized using iodonium ions to form a 2,6-anhydro-2,3-dideoxy-2-octenoate ester having protected hydroxy groups or a 2,6-anhydro-2,3-dideoxy-2-heptenoate ester having protected hydroxy groups, optionally removing the hydroxy protecting groups or replacing them by other hydroxy protecting groups and optionally converting the resulting ester into the free acid, a salt or another ester.

23. A process for preparing a 2,6-anhydro-2,3-dideoxy-D-manno-2-octenoic acid compound of formula 17, or a salt or

ester thereof, in which R is a hydrogen atom, an ester group or a cation and R^1-R^4 independently of each other stand for hydrogen atoms or hydroxy protecting groups, in which a 1,4 cyclic sulfate of a D-mannitol having protected 2-, 3-, 5- and 6-hydroxy groups is reacted with the anion of a glyoxylic acid ester dithioacetal compound of formula 21, in which R is an ester group and R^6 is an alkyl group having 1-6 carbon atoms, a phenyl group or a benzyl group, to form, after hydrolysis of the sulfate group, a compound of formula 22, in which R and R^6 have the above meanings and R^1-R^4 are hydroxy protecting groups, which compound of formula 22 is cyclized using iodonium ions to form a compound of formula 17, optionally removing the hydroxy protecting groups or replacing them by other hydroxy protecting groups and optionally converting the resulting ester into the free acid, a salt or another ester.

24. A process according to claim 23, in which 1,4 cyclic sulfate of 2,3:5,6-di-O-isopropylidene-D-mannitol of formula 2 is reacted with a glyoxylic acid ester dithioacetal compound of formula 14, in which R is an ester group, to form a compound of formula 15 which is cyclized by means of iodonium sym-dicollidine perchlorate to a compound of formula 17, in which R^1+R^2 and R^3+R^4 are hydroxy protecting isopropylidene groups and R is an ester group, optionally removing the hydroxy protecting groups or replacing them by other hydroxy protecting groups and optionally converting the resulting ester into the free acid, a salt or another ester.

25. A process for preparing a 2-deoxy-heptopyranose compound or a 2-deoxy-hexopyranose compound, which process comprises reacting either a 1,4 cyclic sulfate of a D-hexitol having protected 2-, 3-, 5- and 6-hydroxy groups or a 1,4 cyclic sulfate of a D-pentitol having protected 2-, 3- and 5-hydroxy groups, with the anion of a bis (hydrocarbylthio) methane compound, in which the hydrocarbyl group is an alkyl group having 1-6 carbon atoms, a phenyl group or a benzyl group, to form, after hydrolysis of the sulfate group, either a 2-deoxy-heptose bis (hydrocarbylthio) acetal compound having protected 3-,4-,6- and 7-hydroxy groups, or a 2-deoxy-hexose bis (hydrocarbylthio) acetal compound having protected 3-, 4- and 6-hydroxy groups, followed by removal of the dithioacetal group to form a 2-deoxy-heptopyranose compound having protected 3-,4-,6- and 7-hydroxy groups or a 2-deoxy-hexopyranose compound having protected 3-, 4- and 6-hydroxy groups, and optionally removing the hydroxy protecting groups or replacing them by other hydroxy protecting groups.

26. A process for preparing a 2-deoxy-α/β-D-arabino-hexopyranose compound, which process comprises reacting a 1,4 cyclic sulfate of a D-arabinitol having protected 2-, 3- and 5-hydroxy groups, with the anion of a bis (hydrocarbylthio) methane compound, in which the hydrocarbyl group is an alkyl group having 1-6 carbon atoms, a phenyl group or a benzyl group, to form, after hydrolysis of the sulfate group, a 2-deoxy-D-arabino-hexose bis (hydrocarbylthio) acetal compound having protected 3-, 4- and 6-hydroxy groups, followed by

removal of the dithioacetal group to form a 2-deoxy-α/β-D-arabino-hexopyranose compound having protected 3-, 4- and 6-hydroxy groups, and optionally removing the hydroxy protecting groups or replacing them by other hydroxy protecting groups.

27. A process for preparing a 2-deoxy-α/β-D-arabino-hexopyranose compound, which process comprises reacting 1,4 cyclic sulfate of 2,3,5-tri-O-benzyl-D-arabinitol of formula 27 with the anion of bis (methylthio) methane to form, after hydrolysis of the sulfate group, 3,4,6-tri-O-benzyl-2-deoxy-D-arabino-hexose bis (methylthio) acetal of formula 36, followed by removal of the dithioacetal group to form 3,4,6-tri-O-benzyl-2-deoxy-α/β-D-arabino-hexopyranose of formula 40, and optionally removing the hydroxy protecting groups or replacing them by other hydroxy protecting groups.

28. A process for preparing a 2-deoxy-heptono-1,5-lactone compound or a 2-deoxy-hexono-1,5-lactone compound, which process comprises reacting either a 1,4 cyclic sulfate of a D-hexitol having protected 2-, 3-, 5- and 6-hydroxy groups or a 1,4 cyclic sulfate of a D-pentitol having protected 2-, 3- and 5-hydroxy groups, with the anion of a tris (hydrocarbylthio) methane compound, in which the hydrocarbyl group is an alkyl group having 1-6 carbon atoms, a phenyl group or a benzyl group, to form, after hydrolysis of the sulfate group, either a 2-deoxy-heptonic acid hydrocarbylthio orthoacetal compound having protected 3-,4-,6- and 7-hydroxy groups, or a 2-deoxy-hexonic acid hydrocarbylthio orthoacetal compound having protected 3-, 4- and 6-hydroxy groups, followed by removal of

the dithioacetal group to form a 2-deoxy-heptono-1,5-lactone compound having protected 3-,4-,6- and 7-hydroxy groups or a 2-deoxy-hexono-1,5-lactone compound having protected 3-, 4- and 6-hydroxy groups, and optionally removing the hydroxy protecting groups or replacing them by other hydroxy protecting groups.

29. A process for preparing a 2-deoxy-D-arabino-hexono-1,5-lactone compound, which process comprises reacting a 1,4 cyclic sulfate of a D-arabinitol having protected 2-, 3- and 5-hydroxy groups, with the anion of a tris (hydrocarbylthio) methane compound, in which the hydrocarbyl group is an alkyl group having 1-6 carbon atoms, a phenyl group or a benzyl group, to form, after hydrolysis of the sulfate group, a 2-deoxy-D-arabino-hexonic acid hydrocarbylthio orthoacetal compound having protected 3-, 4- and 6-hydroxy groups, followed by removal of the dithioacetal group to form a 2-deoxy-D-arabino-hexono-1,5-lactone compound having protected 3-, 4- and 6-hydroxy groups, and optionally removing the hydroxy protecting groups or replacing them by other hydroxy protecting groups.

30. A process for preparing a 2-deoxy-D-arabino-hexono-1,5-lactone compound, which process comprises reacting 1,4 cyclic sulfate of 2,3,5-tri-O-benzyl-D-arabinitol of formula 27 with the anion of tris (methylthio) methane to form, after hydrolysis of the sulfate group, 3,4,6-tri-O-benzyl-2-deoxy-D-arabino-hexonic acid methylthio orthoacetal of formula 38, followed by removal of the dithioacetal group to form 3,4,6-

tri-O-benzyl-2-deoxy-D-arabino-hexono-1,5-lactone of formula 41, and optionally removing the hydroxy protecting groups or replacing them by other hydroxy protecting groups.

31. A 3-deoxy-octulonate dithioacetal compound having protected 4-,5-,7- and 8-hydroxy groups.

32. A 3-deoxy-heptulonate dithioacetal compound having protected 4-, 5- and 7-hydroxy groups.

33. A compound of formula 22, in which R is an ester group, R^1-R^4 stand for hydroxy protecting groups and R^6 is an alkyl group having 1-6 carbon atoms, a phenyl group or a benzyl group.

34. A compound of formula 15, in which R is an ester group, such as methyl or ethyl.

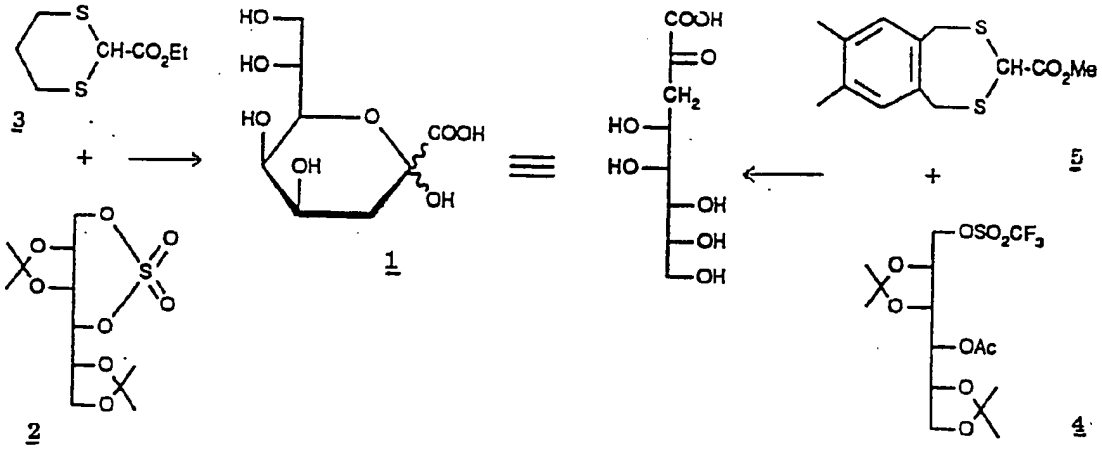
35. A compound of formula 12, in which R is an ester group, such as methyl or ethyl.

36. A compound of formula 34, and corresponding compounds in which the ethyl ester group is replaced by a different ester group.

37. A compound of formula 36, and corresponding compounds in which one or more of the methylthio groups are replaced by a C_{2-6} alkylthio, a phenylthio or a benzylthio group.

38. A compound of formula 38, and corresponding compounds in which one or more of the methylthio groups are replaced by a C_{2-6} alkylthio, a phenylthio or a benzylthio group.

Reaction Scheme A



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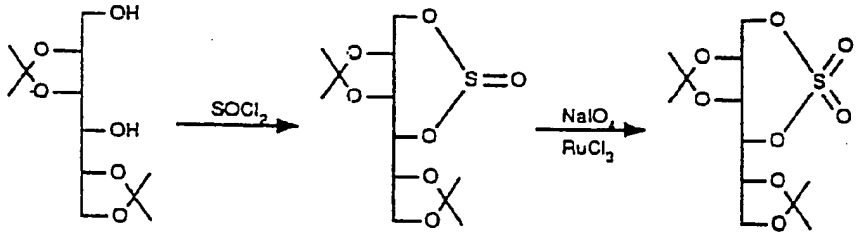

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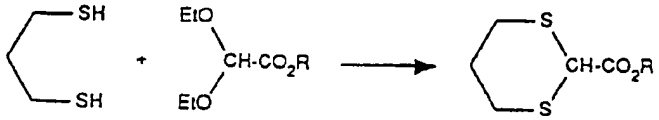

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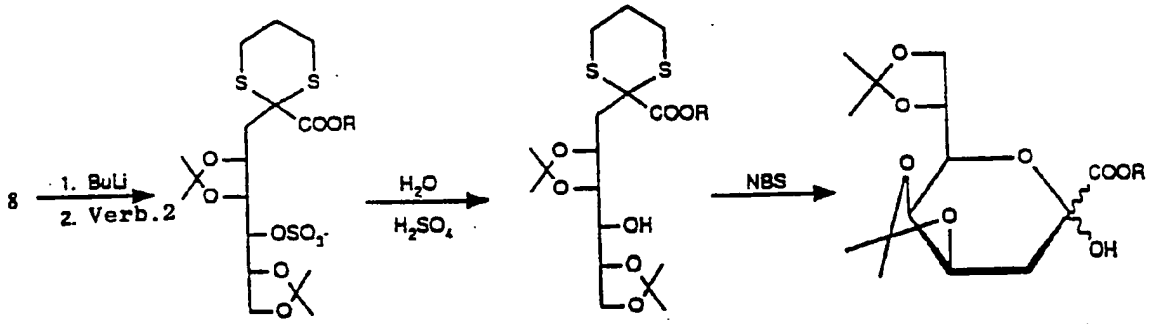
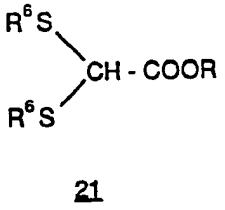


11 12 13



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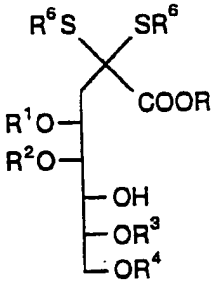

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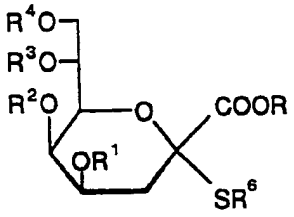

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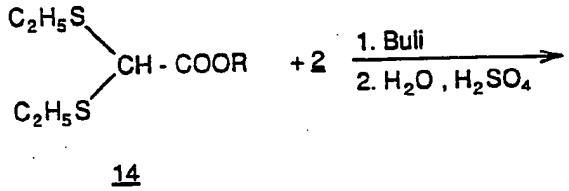

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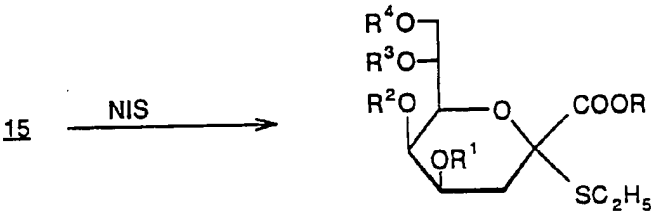
Reaction Scheme F



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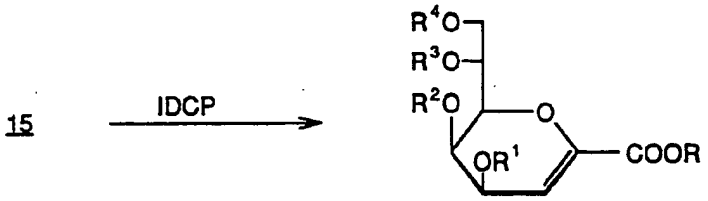
Reaction Scheme G



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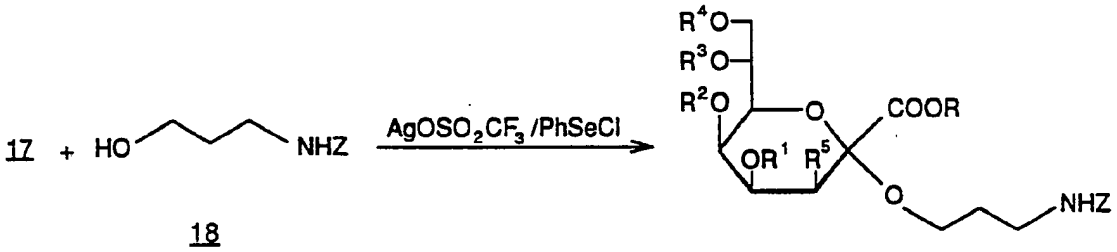
Reaction Scheme H



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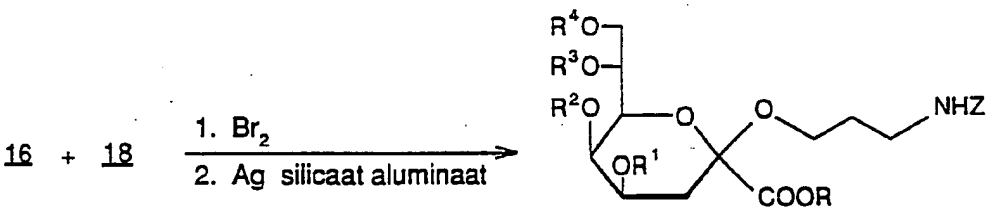
Reaction Scheme I



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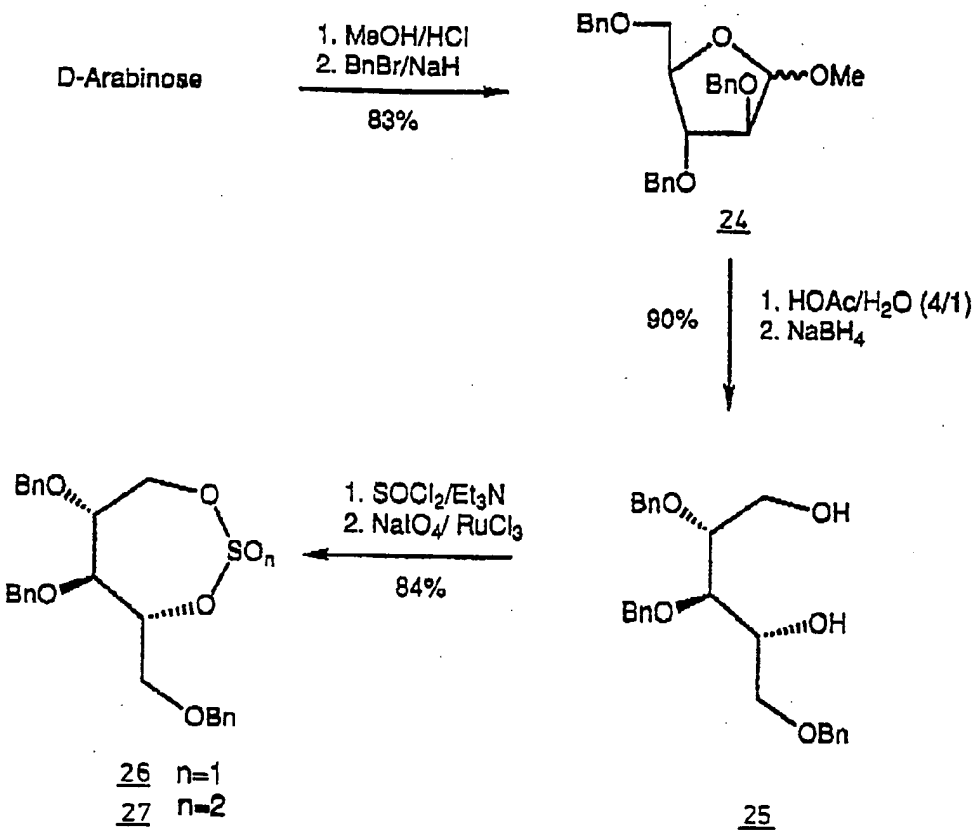

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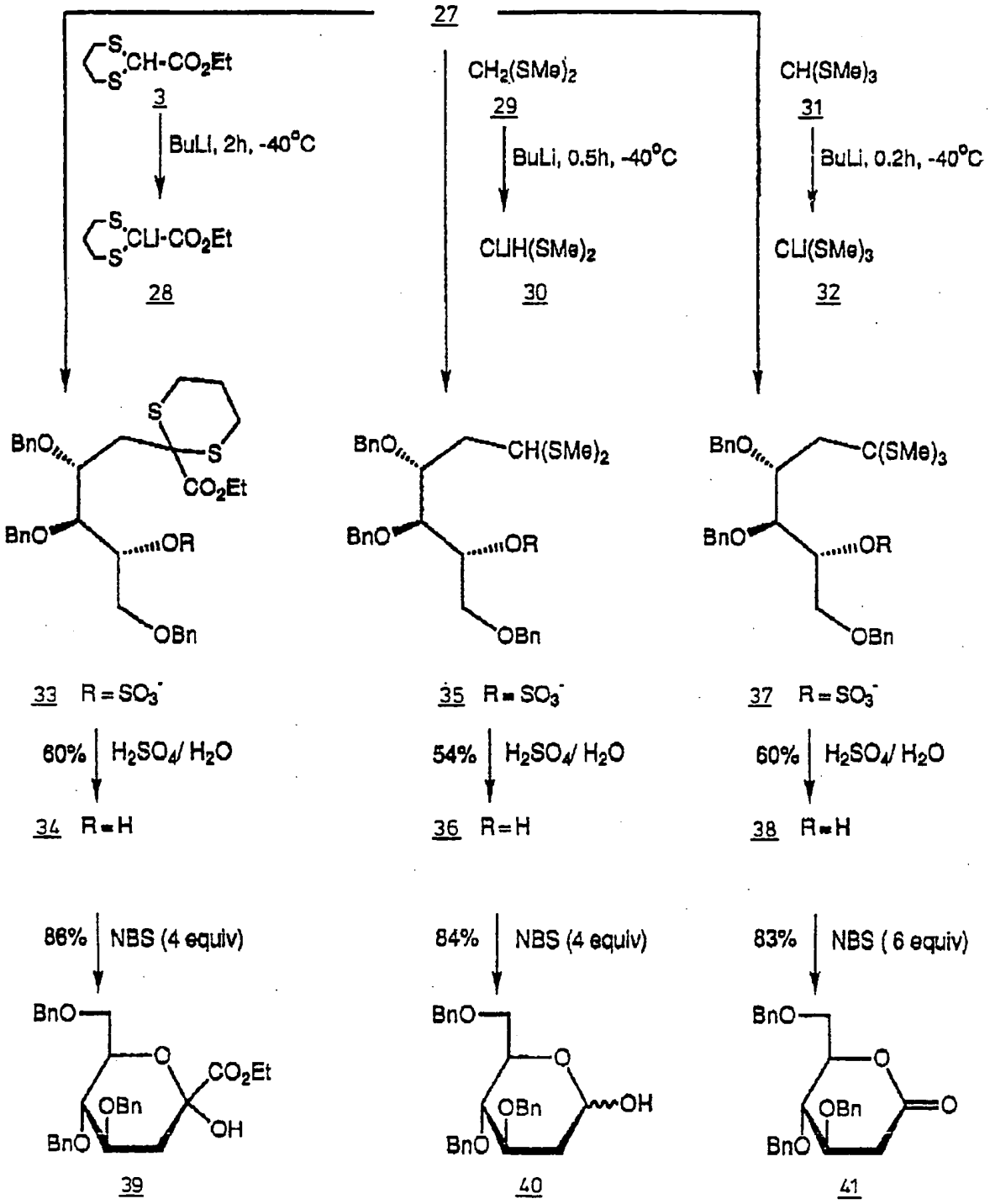

INTERNATIONAL SEARCH REPORT

International Application No PCT/NL 90/00124

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: C 07 H 7/027, 15/14, C 07 D 327/10, 309/30, C 07 C 327/28

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	C 07 H 7/00, 15/00, C 07 D 327/00, 309/00, C 07 C 327/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	Tetrahedron Letters, volume 28, no. 49, 1987, Pergamon Journals Ltd., (GB), M. Imoto et al.: "A new synthesis of 3-deoxy-D-manno-2-octulosonic acid (KDO) from D-mannose", pages 6235-6238, see the whole article (cited in the application)	11-30
Y	FR, A, 2317275 (AKTIEBOLAGET LEO) 4 February 1977 see page 1, line 1 - page 2, line 21; page 14, line 37 - page 15, line 1; page 18, line 28 - page 19, line 4; claims 1,2	11-30
A	J. Am. Chem. Soc., volume 110, 1988, American Chemical Society, Y. Gao et al.: "Vicinal diol cyclic sulfates: like epoxides only more reactive", pages 7538-7539 see the whole article ./.	11-30

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
15th October 1990	08. 11. 90
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme N. KUIPER

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, " with indication, where appropriate, of the relevant passages	Relevant to Claim No.
P,X, Y	Tetrahedron Letters, volume 30, no. 40, 1989, Pergamon Press Plc., P.A.M. van der Klein et al.: "An efficient route to 3-deoxy-d-manno-2 -octulosonic acid (KDO) derivatives via a 1,4-cyclic sulfate approach", pages 5477-5480 see the whole article ---	1-30

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. NL 9000124 SA 39299

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 29/10/90. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR-A- 2317275	04-02-77	GB-A- 1511159	17-05-78
		BE-A- 844018	10-01-77
		CA-A- 1085824	16-09-80
		CA-A- 1088055	21-10-80
		CH-A- 631969	15-09-82
		DE-A- 2629945	27-01-77
		JP-A- 52010201	26-01-77
		SE-A- 7607741	11-01-77
		US-A- 4249002	03-02-81
		US-A- 4249003	03-02-81